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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME:

Vyndaqel®/tafamidis meglumine

PROTOCOL NO.: B3461028

PROTOCOL TITLE:

A Multicenter, International, Phase 3, Double-Blind, Placebo-Controlled, Randomized Study to Evaluate the Efficacy, Safety, and Tolerability of Daily Oral Dosing of Tafamidis Meglumine (PF-06291826) 20 mg or 80 mg in Comparison to Placebo in Subjects Diagnosed With Transthyretin Cardiomyopathy (TTR-CM).

Study Center(s):

This study was conducted at 48 centers in 13 countries: Belgium (1), Brazil (1), Canada (1), Czech Republic (3), France (2), Germany (2), Italy (3), Japan (3), Netherlands (1), Spain (2), Sweden (2), United Kingdom (2), and United States (25).

Study Initiation Date and Primary Completion Date:

Study Initiation Date: = 09 December 2013

Final Completion Date: = 07 February 2018

Phase of Development:

Phase 3

Study Objective:

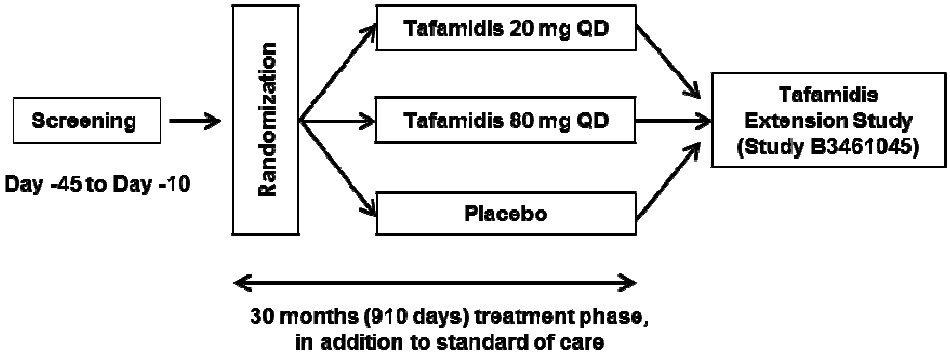
The primary objective of this study was to assess the efficacy of an oral dose of 20 mg or 80 mg tafamidis meglumine soft gel capsules based on all-cause mortality and on frequency of cardiovascular-related hospitalizations, as well as to assess safety and tolerability in comparison to placebo. Tafamidis or placebo was administered once daily (QD), in addition to standard of care, for 30 months in subjects diagnosed with variant or wild-type transthyretin cardiomyopathy (TTR-CM, also known as ATTR-CM).

METHODS

Study Design:

This was a Phase 3, multicenter, international, three-arm, parallel design, placebo-controlled, randomized study with a 30-month double-blind treatment phase, to determine efficacy, safety, and tolerability of tafamidis on clinical outcomes in subjects with either variant or wild-type TTR-CM. The study design is shown in Figure 1.

Figure 1. Schematic Diagram of the Study



The targeted enrollment for the study was 400 subjects to be randomized in a 2:1:2 ratio (placebo:20 mg tafamidis:80 mg tafamidis). The subjects were to be allocated to the 3 arms of the study in the following manner: n=160 in the placebo arm, n=80 in the 20 mg arm, and n=160 in the 80 mg arm. Subjects who experienced adverse events (AEs) associated with poor tolerability to treatment with tafamidis that might impact dosing adherence had the option of blinded treatment re-assignment and potential dose reduction. Subjects were stratified during enrollment for treatment assignment by TTR genotype (variant and wild-type) with the intent of enrolling greater than 30% of randomized subjects with variant TTR-CM and greater than 30% of subjects with wild-type TTR-CM, with the intent to enroll comparable numbers between the variant and wild-type groups.

Additionally, stratification to treatment assignment was done for baseline severity of disease based on New York Heart Association Classification (NYHA) classification (NYHA Class I and NYHA Classes II and III combined). Stratification was implemented to maintain a balance of treatment assignments within both TTR genotype and disease severity.

Subjects were to be treated for 30 months. For the purpose of this study, 30 months was defined as 910 days. For any subject who discontinued prior to 30 months, the site was to ensure a Month 30 follow-up (also called the follow-up period) contact to determine the subject's vital status and whether the subject had a heart and/or liver transplant or implantation of a cardiac mechanical assist device. To achieve this, subjects participating in the trial were required to provide consent for release of medical information to permit access to medical records as well as vital status/transplant status/cardiac mechanical assist device status follow up by the site with the subject or the subject's caregivers 30 months after study randomization in the event that the subject could not be reached.

Upon completion of the study at the Month 30 visit, subjects were eligible for treatment with tafamidis in a separate extension study (B3461045), which permitted the collection of additional safety and efficacy data. Eligibility for the extension study required subject participation in this study at least through Day 896 (Month 30 minus 2 weeks). The schedule of activities shown in Table 1 provides an overview of the protocol visits and procedures.

Table 1. Schedule of Activities

Protocol Activity	Screening Period	Baseline		Month										
	Day -45 to Day -10	Day 1	Week 2[a]	1	3	6	9	12	15	18	21	24	27	30 (Day 910) (or Early Study Discontinuation)
Visit Window (± weeks)			1	1	2	2	2	2	2	2	2	2	2	2
Informed Consent and Release of Medical Information Form	X													
Medical History	X	X												
Smoking and Alcohol Classification	X													
Review entrance criteria		X												
Randomization		X												
Physical examination (full)	X													X
Brief physical examination		X		X	X	X	X	X	X	X	X	X	X	
Height	X													
Weight	X	X		X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG	X	X[b]		X		X		X		X		X		X
Vital signs[c]	X	X		X	X	X	X	X	X	X	X	X	X	X
Echocardiogram	X					X				X				X
Tissue biopsy[d]	X													
Laboratory samples														
Hematology	X	X	X	X		X		X		X		X		X
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation (INR, PT – Local)[e]	X	X		X		X		X		X		X		X
Retinol Binding Protein		X		X		X		X		X		X		X
Serology (HBsAg, anti-HCV, and HIV)	X													
Serum/urine test for primary (light chain) amyloidosis (AL)	X													
Urinalysis	X	X		X		X		X		X		X		X
Genotyping	X													
Pregnancy test[f]	X	X		X		X		X		X		X		X
TTR stabilization, TTR oligomer concentration, and TTR concentration[g]		X		X		X		X		X		X		X

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Protocol Activity	Screening Period	Baseline		Month										
	Day -45 to Day -10	Day 1	Week 2[a]	1	3	6	9	12	15	18	21	24	27	30 (Day 910) (or Early Study Discontinuation)
Urine TTR oligomer concentration[h]								X		X		X		X
Tafamidis concentrations[i]		X		X		X		X		X		X		X
Tafamidis concentrations (for subjects receiving dialysis or hemofiltration)[j]			Any time during the study											
Diflunisal concentration[k]	X	X		X		X				X				X
Pharmacogenetic sample		X												
NT – proBNP, troponin I	X	X						X						X
6MWT	X	X				X		X		X		X		X
KCCQ[l]		X				X		X		X		X		X
EQ-5D-3L[m]		X				X		X		X		X		X
PGA[n]		X				X		X		X		X		X
NYHA classification	X	X				X		X		X		X		X
Concomitant medications[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record time of dosing				X		X		X		X		X		X
Record dosing adherence				X	X	X	X	X	X	X	X	X	X	X
Adverse Events reporting		X	X	X	X	X	X	X	X	X	X	X	X	X[p]
Hospitalization determination		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense blinded medication		X			X	X	X	X	X	X	X	X	X	
Documentation of vital transplant and implant status[q]		X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception Discussion[r]	X	X		X	X	X	X	X	X	X	X	X	X	

Abbreviations: 6MWT = 6-Minute Walk Test; ECG = Electrocardiogram; EQ-5D-3L = EuroQOL-5 Dimensions (3 Levels version); HBsAg = serology for hepatitis B; HCV = Hepatitis C virus; HIV = Human Immunodeficiency Virus; INR = International Normalized Ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-Terminal prohormone B-type Natriuretic Peptide; NYHA = New York Heart Association Classification; PGA = Patient Global Assessment; PT = prothrombin time; TTR = Transthyretin.

a. The Week 2 "visit" allowed the subject to either come to the clinic, or consisted of a telephone call to the subject for specified data determination and had the subject go to a local laboratory or local physician's office to have their needed laboratory samples collected and shipped to the central laboratory.

b. Baseline (Day 1) ECG pre dose.

c. Systolic and diastolic blood pressure and pulse rate (supine at least 3 minutes and standing at least 2 minutes prior to assessment), respiration rate and body temperature.

Table 1. Schedule of Activities

Protocol Activity	Screening Period	Baseline		Month										
	Day -45 to Day -10	Day 1	Week 2[a]	1	3	6	9	12	15	18	21	24	27	30 (Day 910) (or Early Study Discontinuation)

d. Biopsy was performed at Screening or had been performed and documented previously.
e. INR and PT were determined at the site's local laboratory.
f. For women of childbearing potential. Pregnancy tests were repeated as per request of IRB/IECs or if required by local regulations.
g. TTR stabilization, TTR oligomer concentration, and TTR concentration: Baseline (Day 1) sample: collected at any time pre dose during the clinic visit. Month 1 sample: collected pre dose and at 3 hours (± 1.5 hours) post dose; Month 6 sample: collected at 7 hours (+ 2.5 hours) post dose; Month 12 sample: collected at 7 hours (± 2.5 hours) post dose; Month 18 sample: collected at 1 hour (± 30 minutes) post dose; Month 24 sample: collected at 1 hour (±30 minutes) post dose; Month 30 sample: collected at any time during clinic visit.
h. Subjects at selected centers provided a urine sample to be used in assay development for measurement of TTR oligomer concentrations in urine. For those subjects who provided consent, a 10 mL aliquot of urine was collected (starting at the earliest possible prospective visit for the subject) at Months 12, 18, 24, and 30 (or Early Study Discontinuation); this aliquot was obtained from the urine sample already collected for urinalysis at these visits.
i. Baseline (Day 1) tafamidis concentration sample: collected at any time pre dose during the clinic visit. Month 1 tafamidis concentration sample: collected pre dose and at 3 hours (±1.5 hours) post dose; Month 6 tafamidis concentration sample: collected at 7 hours (± 2.5 hours) post dose; Month 12 tafamidis concentration samples: collected at 7 hours (± 2.5 hours) post dose; Month 18 tafamidis concentration sample: collected at 1 hour (± 30 minutes) post dose; Month 24 tafamidis concentration sample: collected at 1 hour (± 30 minutes) post dose; Month 30 tafamidis concentration: collected at any time during the clinic visit.
j. If a subject required dialysis or hemofiltration at any time after randomization while on study treatment, the subject should have had blood samples collected for tafamidis concentrations around the time of renal replacement therapy. The timing of the sample collection would depend on the type of renal replacement therapy administered. For hemodialysis or hemofiltration, samples should have been collected on the date of the renal replacement therapy both prior to administration and after administration. If peritoneal dialysis was administered, the first sample should have been collected at initiation of the first exchange. The second sample should have been collected after the first exchange was completed (if performed outside of the home) or at least 24 hours after the initiation of the first exchange (if administered at home). Every effort should have been made to collect these samples on the date of the subject's first administration of renal replacement therapy in the study; however, if this was not possible, the samples should have been obtained as soon as possible on the date of a renal replacement therapy treatment. If necessary, the sample collection could have been obtained using the guidelines for lab sample collection in the Guidance for Remotely Conducted Study Visits provided for the study. At the time of sample collection, the date and time of the last dose and the date and time of sample collection was recorded.
k. Diflunisal concentration to determine if there was evidence of exposure to diflunisal prior to or during the study. Sample was collected at any time during the clinic visit, after the ECG blood pressure and vital signs.
l. Kansas City Cardiomyopathy Questionnaire (KCCQ) was completed before the EQ-5D-and PGA.
m. EuroQoL 5 Dimensions (3 Levels version) (EQ-5D-3L) was completed after the KCCQ.
n. Patient Global Assessment (PGA) was completed after the KCCQ and EQ-5D-3L.
o. At the Screening visit, this was prior medications.

Table 1. Schedule of Activities

Protocol Activity	Screening Period	Baseline		Month										
	Day -45 to Day -10	Day 1	Week 2[a]	1	3	6	9	12	15	18	21	24	27	30 (Day 910) (or Early Study Discontinuation)

p. Except for subjects who are randomized into the extension study (Study B3461045), all other subjects had a 4 week (28 calendar days) safety follow up visit after the last dose of the study medication for collection of adverse events. This visit could have been completed by telephone.
q. When the Vital Status was determined, the subject was asked if they had undergone a heart and/or liver transplant or implantation of cardiac mechanical assist device. This was especially important at the 30 month visit. If a subject indicated that they had a transplant and they were still enrolled in the study, they should have been removed from the study.
r. For all subjects who, in the opinion of the investigator, were biologically capable of having children and were sexually active; at each study visit, the need to use highly effective contraception consistently and correctly was discussed with the subject, the subject was instructed to call immediately if a selected birth control method was discontinued or if pregnancy was known or suspected and such conversation documented in the patient chart.

Number of Subjects (Planned and Analyzed):

The targeted enrollment for this study was 400 subjects to be randomized in a 2:1:2 ratio (placebo:20 mg tafamidis:80 mg tafamidis). The subjects were to be allocated to the 3 arms of the study in the following manner: n=160 in the placebo arm, n=80 in the 20 mg arm, and n=160 in the 80 mg arm. Of the 548 subjects screened for entry into the study, 441 were randomized into treatment. This included 88 subjects randomized into the tafamidis 20 mg group, 176 subjects randomized into the tafamidis 80 mg group, and 177 subjects randomized into the placebo group. All randomized subjects received at least 1 dose of study drug (safety analysis set).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Eligible subjects were between 18 and 90 years old at the time of randomization, willing to sign an informed consent and release of Medical Information Form and comply with scheduled visits, treatment plan, laboratory tests and other study procedures. In order to qualify for this study, all potentially eligible subjects were required to have a medical history of heart failure with at least 1 prior hospitalization for heart failure or clinical evidence of heart failure (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures (eg, elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral edema) that required treatment with a diuretic for improvement, evidence of cardiac involvement by echocardiography with an end diastolic interventricular septal wall thickness >12 mm, and presence of amyloid deposits in biopsy tissue and presence of a variant TTR genotype and/or TTR precursor protein identification by immunohistochemistry, scintigraphy or mass spectrometry.

Exclusions for the study included subjects with: symptoms indicative of NYHA Classification IV at the Screening or Baseline visit, primary (light chain) amyloidosis and prior liver or heart transplantation, or implanted cardiac mechanical assist device.

Study Treatment:

Subjects were assigned to blinded treatment with either tafamidis 20 mg or 80 mg or matching placebo capsules QD, in addition to standard of care (eg, diuretics) for 30 months. In order to achieve the proper dosage and maintain the blind in the study, capsules were dispensed in a blinded fashion to achieve a daily dose of 4 capsules. Each dose of 4 capsules consisted of either 3 capsules of matching blinded placebo and 1 capsule of blinded tafamidis 20 mg, 4 capsules of blinded tafamidis 20 mg, or 4 capsules of matching blinded placebo. In the event of a dose reduction, the dose consisted of 2 capsules of blinded tafamidis 20 mg and 2 capsules of matching blinded placebo.

Efficacy Endpoints:

Primary Analysis

The primary analysis used a hierarchical combination, applying the method of Finkelstein-Schoenfeld to:

1. All-cause mortality and

2. Frequency of cardiovascular-related hospitalizations over the duration of the trial, which was defined as the number of times a subject was hospitalized (ie, admitted to a hospital) for cardiovascular-related morbidity.

Subjects who discontinued for transplantation (ie, heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device were handled in the primary analysis in the same manner as death.

Key Secondary Endpoints

1. Change from Baseline to Month 30 in the distance walked during 6-Minute Walk Test (6MWT).

2. Change from Baseline to Month 30 in the Kansas City Cardiomyopathy Questionnaire (KCCQ) - Overall Summary (OS) score.

Secondary Endpoints

1. Cardiovascular-related mortality.

2. Frequency of cardiovascular-related hospitalization.

3. All-cause mortality.

4. TTR stabilization at Month 1.

Safety Evaluations:

Safety and tolerability were assessed in comparison to placebo with AE reporting as well as the conduct of electrocardiograms (ECGs), clinical laboratory testing, vital signs, and physical examinations. The safety analysis set included all subjects who were enrolled (randomized) and received at least 1 dose of double-blind medication.

Statistical Methods:

The safety analysis set included all randomized subjects who received at least 1 dose of study drug. The intent-to-treat (ITT) analysis set included all subjects in the safety analysis set who had at least 1 post-baseline efficacy evaluation (ie, post-baseline hospitalization, study visit, or date of death). The per protocol (PP) analysis set included all subjects in the ITT set who did not violate inclusion/exclusion criteria and who did not have protocol violations considered to impact the interpretation of the primary efficacy analysis.

Primary Analysis

The primary analysis used a hierarchical combination applying the method of Finkelstein-Schoenfeld to all-cause mortality and frequency of cardiovascular-related hospitalizations (which is defined as the number of times a subject was hospitalized [ie, admitted to a hospital] for cardiovascular-related morbidity) over the duration of the trial. Subjects, who discontinued for transplantation (ie, heart transplantation and combined heart

and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the primary analysis in the same manner as death. The primary analysis combined the subjects in the tafamidis 20 mg and tafamidis 80 mg groups (including subjects in the 80 mg group that may have had a dose reduction to 40 mg) into 1 pooled group. This pooled tafamidis group was compared with the placebo group.

Key Secondary Analyses

The key secondary endpoints were evaluated using a mixed model repeated measures analysis of covariance (ANCOVA).

To maintain the type 1 error rate at or below the specified level, a pre-specified hierarchical order for testing of the primary analysis and then key secondary endpoints as indicated above was used to maintain the overall alpha at 0.05 for the primary analysis and the two key secondary endpoints. The multiplicity procedure was applied to the ITT analysis set only.

Statistical significance of the key secondary analyses was dependent on first achieving statistically significant results in the primary analysis ($p \leq 0.05$). If the p-value of the primary analysis was >0.05, then statistical significance could not be achieved for the subsequent tests on 6MWT and KCCQ-OS score. In this hierarchical approach of key secondary endpoints, the change from baseline to Month 30 in distance walked during the 6MWT was first tested at the 0.05 level. If the p-value for the test of 6MWT was ≤0.05, the second variable in the list, the change from baseline to Month 30 in the KCCQ-OS score was tested at the 0.05 level. If the p–value of the test for 6MWT was >0.05, then statistical significance could not be achieved for the subsequent test on KCCQ-OS score.

Secondary Analyses

The "cardiovascular-related mortality" in all analyses, unless otherwise specified, combined deaths adjudicated as cardiovascular-related with deaths adjudicated as indeterminate.

The cardiovascular-related mortality and all-cause mortality were analyzed using survival analysis methods.

Frequency of cardiovascular-related hospitalizations was analyzed using the Poisson regression analyses.

All the analyses on the secondary endpoints described above are additionally presented by TTR genotype (variant and wild-type), NYHA baseline classification, as well as dose (randomized dose group) and were considered exploratory.

The proportion of subjects who achieved TTR stabilization in each treatment group at Month 1 was compared using a Cochran-Mantel-Haenszel test.

A similar test of proportion was done on TTR stabilization at all other time points and was considered exploratory. No subgroup analyses were done at these other time points.

Except for the analyses by dose group, all analyses of the secondary endpoints, including the proposed exploratory analyses of these endpoints compared the pooled tafamidis group with the placebo group.

Safety Analysis

The following 3-tier approach was used to summarize AEs. Under this approach, AEs were classified into 1 of 3 tiers. While the AEs were additionally analyzed by subgroups, the 3-tier approach only applied to the overall AE analyses.

- Tier-1 events: These were pre-specified events of clinical importance and were maintained in a list in the product's Safety Review Plan. This list was updated as more was understood about the drug.

- Tier-2 events: These were events that were not Tier-1 but were "common." A Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) was defined as a Tier-2 event if there were at least 4 in any treatment group.

- Tier-3 events: These were events that were neither Tier-1 nor Tier-2 events.

The analysis of AEs under the 3-tier approach was considered exploratory. There was no adjustment for multiple comparisons or stratification factors in the analyses. For Tier-1 and Tier-2 events, the proportion of AEs observed in each of the treatment groups was presented along with the point estimates and associated 95% confidence intervals of the risk difference for the pooled tafamidis group compared with placebo.

For Tier-1 events, p-values were included in the presentations. AEs were arranged in the output sorted in descending point estimate of the risk difference within system organ class. Footnotes in the outputs included the methods used to derive any p-values and confidence intervals as per Pfizer standards. The Tier 1 AEs were analyzed using the approach of Chang and Zhang who inverted two 1-sided tests at half the significance level each for calculating p-values and confidence intervals.

For Tier 2 AEs, both proportion and 95% confidence intervals (CIs) were generated using an asymptotic approach (Proc Binomial). A MedDRA PT was defined as a Tier-2 event if there were at least 4 in any treatment group. A cross-industry expert team on safety planning, evaluation, and reporting suggested to use the "Rule of 4" to define Tier-2 events. The "Rule of 4" states that if a trial has 400 or fewer subjects per group and there are 4 or more subjects with a given MedDRA PT in any treatment group, then that PT will be categorized as a Tier-2 event.

For Tier 3 events, simple proportions were presented.

RESULTS

Subject Disposition and Demography:

A summary of subject disposition is provided in Table 2. Of the 548 subjects screened for entry into the study, 441 were randomized into treatment. This included 88 subjects

randomized into the tafamidis 20 mg group, 176 subjects randomized into the tafamidis 80 mg group, and 177 subjects randomized into the placebo group. Subjects were stratified by TTR genotype and NYHA baseline classification. All randomized subjects received at least 1 dose of study drug (safety analysis set). A total of 6 subjects requested a blinded dose reduction: 2 in the tafamidis 80 mg group and 4 in the placebo group. Of the 441 subjects included in the safety analysis set, 258 (58.5%) completed the study and 106 (24.0%) discontinued the study.

Table 2. Subject Disposition

Number (%) of Subjects	Tafamidis 20 mg n (%)	Tafamidis 80 mg n (%)	Pooled Tafamidis n (%)	Placebo n (%)	Total[a] n (%)
Assigned to study treatments	88	176	264	177	441
Treated	88 (100.0)	176 (100.0)	264 (100.0)	177 (100.0)	441 (100.0)
Completed[b]	60 (68.2)	113 (64.2)	173 (65.5)	85 (48.0)	258 (58.5)
Discontinued[c]	14 (15.9)	38 (21.6)	52 (19.7)	54 (30.5)	106 (24.0)
Death	14 (15.9)	25 (14.2)	39 (14.8)	38 (21.5)	77 (17.5)
Analyzed for Efficacy					
ITT Analysis set	88 (100.0)	176 (100.0)	264 (100.0)	177 (100.0)	441 (100.0)
Per-Protocol Analysis set	84 (95.5)	171 (97.2)	255 (96.6)	169 (95.5)	424 (96.1)
Analyzed for Safety[d]	88 (100.0)	176 (100.0)	264 (100.0)	177 (100.0)	441 (100.0)
Adverse events[e]	87 (98.9)	175 (99.4)	262 (99.2)	175 (98.9)	437 (99.1)
Laboratory data[f]	88 (100.0)	176 (100.0)	264 (100.0)	177 (100.0)	441 (100.0)

Abbreviations: ITT = intent-to-treat; n = number of subjects.

a. Total = pooled tafamidis + placebo.
b. The number of subjects completed is derived from the subject summary electronic case report form.
c. Discontinued from study other than death.
d. Analyzed for safety tabulates the number of subjects treated.
e. Adverse events tabulates the number of subjects who have reported an AE.
f. Laboratory data tabulates the number of subjects who have at least 1 lab result.

A summary of demographic and baseline characteristics for the ITT analysis set is provided in Table 3. Overall, the baseline characteristics of the tafamidis and placebo groups were similar.

Table 3. Demographic and Baseline Characteristics (ITT Analysis Set)

	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)	Pooled Tafamidis (N=264)	Placebo (N=177)
Age (years)[a]				
n	88	176	264	177
Mean (SD)	73.3 (7.07)	75.2 (7.24)	74.5 (7.23)	74.1 (6.69)
Min, Max	51, 86	46, 88	46, 88	51, 89
Sex n (%)				
Male	83 (94.3)	158 (89.8)	241 (91.3)	157 (88.7)
Female	5 (5.7)	18 (10.2)	23 (8.7)	20 (11.3)
Height(cm)				
n	88	176	264	177
Mean (SD)	176.41 (7.908)	174.07 (9.486)	174.85 (9.044)	173.99 (9.480)
Min, Max	155.3, 200.0	139.3, 200.0	139.3,200.0	144.8, 196.0
Weight (kg)				
n	88	176	264	177
Mean (SD)	80.92 (13.469)	80.01 (15.226)	80.31 (14.644)	79.74 (14.380)
Min, Max	46.5, 115.8	42.0, 133.8	42.0,133.8	41.7, 131.0
BMI (kg/m^2)[b]				
n	88	176	264	177
Mean (SD)	26.03 (3.656)	26.32 (3.805)	26.22 (3.752)	26.33 (4.277)
Min, Max	16.0, 35.0	18.0, 40.0	16.0, 40.0	16.0, 48.0
mBMI[c]				
n	88	176	264	177
Mean (SD)	1047.45 (176.733)	1064.46 (172.484)	1058.79 (173.761)	1066.40 (194.444)
Min, Max	646.0, 1505.0	621.0, 1584.0	621.0, 1584.0	608.0, 1728.0
Race – n (%)				
White	75 (85.2)	136 (77.3)	211 (79.9)	146 (82.5)
Black	11 (12.5)	26 (14.8)	37 (14.0)	26 (14.7)
Asian	2 (2.3)	11 (6.3)	13 (4.9)	5 (2.8)
Other	0	3 (1.7)	3 (1.1)	0
Ethnicity – n (%)				
Hispanic/ Latino	3 (3.4)	4 (2.3)	7 (2.7)	7 (4.0)
Not Hispanic/ Latino	84 (95.5)	171 (97.2)	255 (96.6)	170 (96.0)
Unspecified	1 (1.1)	1 (0.6)	2 (0.8)	0
NYHA Baseline Classification,[d] n (%)				
NYHA Class I	8 (9.1)	16 (9.1)	24 (9.1)	13 (7.3)
NYHA Class II	57 (64.8)	105 (59.7)	162 (61.4)	101 (57.1)
NYHA Class III	23 (26.1)	55 (31.3)	78 (29.5)	63 (35.6)
Baseline Stratification – n (%)[d]				
NYHA Class I and II	65 (73.9)	121 (68.8)	186 (70.5)	114 (64.4)
NYHA Class III	23 (26.1)	55 (31.3)	78 (29.5)	63 (35.6)
Wild Type TTR Genotype	67 (76.1)	134 (76.1)	201 (76.1)	134 (75.7)
Variant TTR Genotype	21 (23.9)	42 (23.9)	63 (23.9)	43 (24.3)
Variant TTR Genotype / NYHA Class I and II	12 (13.6)	22 (12.5)	34 (12.9)	24 (13.6)
Variant TTR Genotype / NYHA Class III	9 (10.2)	20 (11.4)	29 (11.0)	19 (10.7)
Wild Type TTR Genotype / NYHA Class I and II	53 (60.2)	99 (56.3)	152 (57.6)	90 (50.8)
Wild Type TTR Genotype / NYHA Class III	14 (15.9)	35 (19.9)	49 (18.6)	44 (24.9)

Table 3. Demographic and Baseline Characteristics (ITT Analysis Set)

	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)	Pooled Tafamidis (N=264)	Placebo (N=177)
Smoking Classification n (%)				
Never Smoked	47 (53.4)	93 (52.8)	140 (53.0)	104 (58.8)
Ex-Smoker	36 (40.9)	72 (40.9)	108 (40.9)	62 (35.0)
Smoker	1 (1.1)	7 (4.0)	8 (3.0)	7 (4.0)
Unspecified	4 (4.5)	4 (2.3)	8 (3.0)	4 (2.3)
Number of Pack Cigarettes (Year)[e]				
n	5	8	13	11
Mean (SD)	33.60 (16.134)	24.48 (31.828)	27.98 (26.439)	20.27 (16.851)
Min, Max	14.0, 53.0	1.5, 97.5	1.5, 97.5	0, 50.0
Number of Pack Tobacco (Year)[e]				
n	1	1	2	3
Mean	14.00	1.50	7.75	22.50
Min, Max	14.0, 14.0	1.5, 1.5	1.5, 14.0	0, 42.0

Abbreviations: BMI = Body Mass Index; ITT = intent-to-treat; DOB = date of birth; mBMI = modified body mass index; Min = Minimum; Max = Maximum; n = number of subjects, N = total number of subjects; NYHA = New York Heart Association classification; SD = Standard Deviation; TTR = Transthyretin

a. Age at screening. Age is calculated as screening date year – birth year. If the screening date month is less than the DOB month, or the screening date month = DOB month and the screening date day is less than the DOB day, then age = (screening date year - DOB year) –1.
b. BMI is defined as weight/(height*0.01)**2.
c. The modified BMI (mBMI) is calculated by multiplying the body mass index [weight (kg)/height (meters squared)] by serum albumin concentration (g/L).
d. NYHA class: I = without resulting limitations, II = slight limitation, III = marked limitation, IV = inability to carry on any physical activity without discomfort. Given the very low number of enrolled subjects with a baseline classification of NYHA Class I, the baseline groupings used for efficacy analyses were changed from 'NYHA Class I and NYHA Classes II and II combined' to NYHA Classes I and II combined and NYHA Class III'.
e. Formula for pack years cigarettes = (average number of cigarettes per day divided by 20) x years of smoking. Formula for pack years tobacco = ounces per week x 2 divided by 7 x years of smoking.

Efficacy Results:

Primary Analysis

The primary analysis used a hierarchical combination applying the method of Finkelstein-Schoenfeld to:

- All-cause mortality, and
- Frequency of cardiovascular-related hospitalizations over the duration of the trial, which was defined as the number of times a subject was hospitalized (ie, admitted to a hospital) for cardiovascular-related morbidity.

The Finkelstein-Schoenfeld method is based on the combination of all-cause mortality and cardiovascular-related hospitalization frequency and gives higher priority to mortality. The

method is based on a pairwise ranking procedure and only uses cardiovascular-related hospitalization frequency when the 2 given subjects are not able to be ranked based on mortality. The Finkelstein-Schoenfeld analysis was applied by 2 strata (TTR genotype and NYHA baseline classification) and combined to produce the overall test statistic. As a result, subject to subject pairwise comparisons were done within the group of similarly severe subjects and then combined.

Subjects who discontinued for transplantation (ie, heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device were handled in the primary analysis in the same manner as death.

Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of cardiovascular-related hospitalizations for the ITT analysis set is provided in Table 4. The primary analysis of the pooled active treatment demonstrated a statistically significant and clinically meaningful treatment effect favoring tafamidis (p=0.0006). The percentage of subjects alive at Month 30 in the pooled tafamidis and placebo groups was 70.5% and 57.1%, respectively. The average frequency per year of cardiovascular-related hospitalizations through Month 30 among subjects alive at Month 30 was 0.297 for the pooled tafamidis group and 0.455 for the placebo group. The descriptive mean was not adjusted for covariates. The model-based covariate-adjusted means for cardiovascular-related hospitalization frequency are presented in Table 7.

Table 4. Finkelstein-Schoenfeld Analysis of All-Cause Mortality and Frequency of Cardiovascular Related Hospitalizations by Pooled Active Treatment (ITT Analysis Set)

	Pooled Tafamidis (N=264)	Placebo (N=177)
Number of subjects alive, n (%)	186 (70.5)	101 (57.1)
Average CV-related hospitalizations during 30 months (per year) among those alive at Month 30[a]	0.297	0.455
p-value from Finkelstein-Schoenfeld method[b]	0.0006	

Abbreviations: CV = Cardiovascular; ITT = intent-to-treat; N = total number of subjects; n = number of subjects.
Note: Only CV-related hospitalizations where the subject is admitted to a hospital over the duration of the trial are included in this analysis; any hospitalizations prior to randomization date are not included.

a. CV-related hospitalizations per year is calculated as (Subject's number of CV related hospitalizations) / (duration on study in years).
b. The Finkelstein-Schoenfeld test is a hierarchical comparison of mortality and CV-hospitalization. Each subject in the clinical study is compared with every other subject within each stratum in a pairwise manner (4 stratum based on NYHA Class and TTR genotype). Subjects, who discontinued for transplantation (ie, heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the primary analysis in the same manner as death stratum in a pairwise manner. The primary comparison tests if at least 1 and possibly both all-cause mortality and frequency of CV related hospitalizations are different between the tafamidis and placebo treatment groups.

The 2 components of the Finkelstein-Schoenfeld analysis, all-cause mortality and frequency of cardiovascular-related hospitalization, were analyzed separately as secondary endpoints but are presented below in order to aid understanding of the primary analysis.

A summary of mortality and hospitalizations for all subjects is provided in Table 5. The occurrences of death were higher in the placebo group (72 [40.7%] subjects) than in the pooled tafamidis group (72 [27.3%] subjects) (heart transplants and cardiac mechanical assist devices not treated as death). Total subjects hospitalized were similar in the pooled tafamidis and placebo groups (190 [72.0%] and 136 [76.8%] subjects, respectively).

Table 5. Summary of Mortality and Hospitalizations for Efficacy Analysis (ITT Analysis Set)

	Tafamidis 20 mg (N=88) n (%)	Tafamidis 80 mg (N=176) n (%)	Pooled Tafamidis (N=264) n (%)	Placebo (N=177) n (%)
All Subjects:				
Total Deaths[a]	23 (26.1)	49 (27.8)	72 (27.3)	72 (40.7)
CV-related	17 (19.3)	36 (20.5)	53 (20.1)	50 (28.2)
Indeterminate	1 (1.1)	4 (2.3)	5 (1.9)	9 (5.1)
Non-CV-related	5 (5.7)	9 (5.1)	14 (5.3)	13 (7.3)
Total Hospitalized[b]	65 (73.9)	125 (71.0)	190 (72.0)	136 (76.8)
CV-related	42 (47.7)	96 (54.5)	138 (52.3)	107 (60.5)
Indeterminate	1 (1.1)	2 (1.1)	3 (1.1)	0
Non-CV-related	44 (50.0)	81 (46.0)	125 (47.3)	80 (45.2)
Heart Transplants[c]	1 (1.1)	6 (3.4)	7 (2.7)	4 (2.3)
Cardiac Mechanical Assist Device Implantation	0	2 (1.1)	2 (0.8)	0

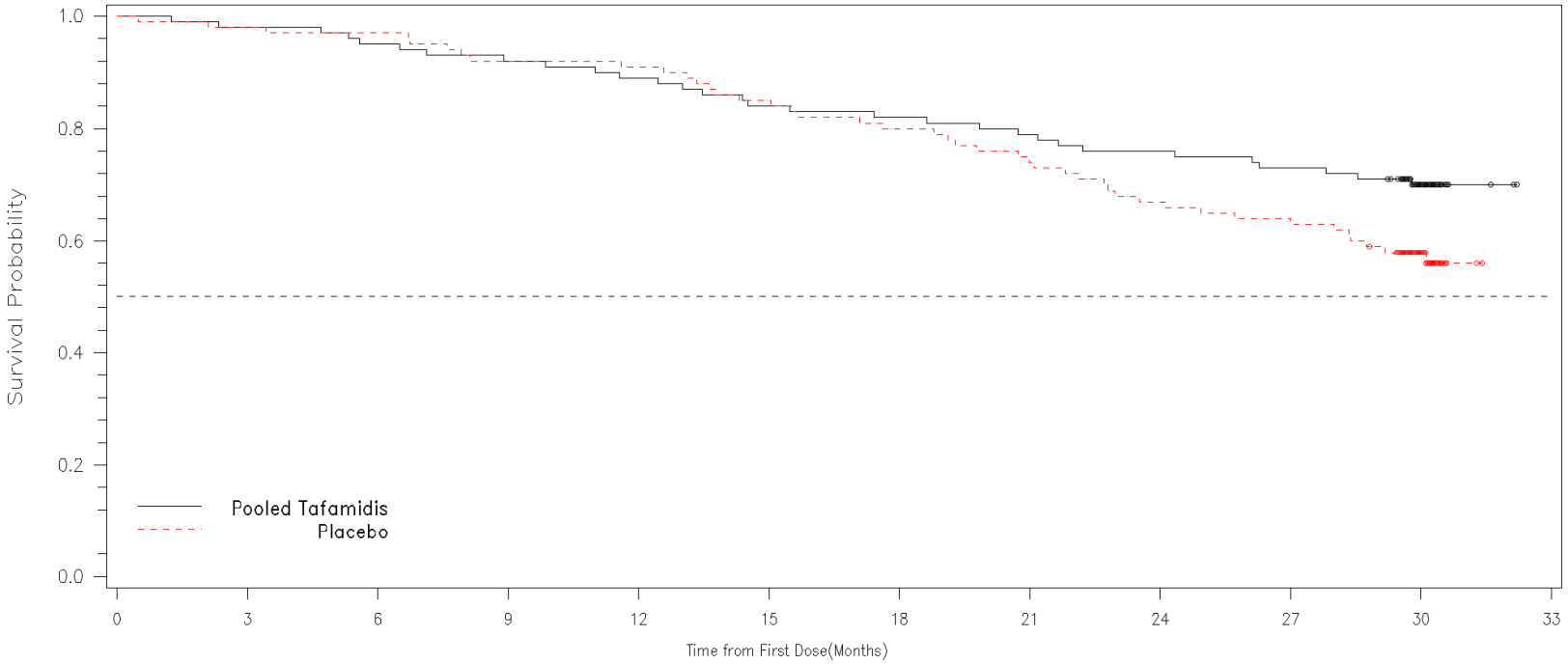
Abbreviations: CV = cardiovascular; ITT = intent-to-treat; N = total number of subjects; n = number of subjects.
Note: CV-related as determined by Adjudication Committee.
a. Deaths (Notice of Death case report form recorded) up to 30 months post randomization are counted.
b. Hospitalizations where the subject is admitted to a hospital over the duration of the trial are included in this analysis; any hospitalizations prior to randomization date are not included. A subject may be counted for each category of hospitalization that applies.
c. Heart Transplants include heart and heart-combo transplantations.

A Kaplan-Meier plot of time to event all-cause mortality with heart transplants and cardiac mechanical assist devices treated as death is presented in Figure 2.

Table 6 presents the results from the analysis of time to event all-cause mortality for ITT analysis set (heart transplants and cardiac mechanical assist devices treated as death). This analysis treats the 7 (2.7%) and 4 (2.3%) heart transplants in the pooled tafamidis and placebo groups, respectively, and the 2 (0.8%) cardiac mechanical assist device implantations in the pooled tafamidis group as death. Overall, all-cause mortality for the pooled tafamidis and placebo groups was 78 (29.5%) and 76 (42.9%) subjects, respectively. There were 186 (70.5%) and 101 (57.1%) subjects in the pooled tafamidis and placebo groups, respectively, censored because they were alive at the time of analysis. The hazard ratio from the all-cause mortality Cox-proportional hazard model for pooled tafamidis was 0.698 (95% CI 0.508, 0.958), indicating a 30.2% reduction in the risk of death relative to the

placebo group (p=0.0259). The observed effect on overall survival emerged after approximately 18 months of treatment (Figure 2).

Figure 2. Kaplan-Meier Plot of Time to Event All-Cause Mortality[a] - Pooled Active Treatment (ITT Analysis Set)



Subjects Remaning at Risk
(Cumulative Events)

Tafamidis	264	259	252	244	235	222	216	209	200	193	99	0
	0	5	12	20	29	42	48	55	64	71	78	78
Placebo	177	173	171	163	161	150	141	131	118	113	51	0
	0	4	6	14	16	27	36	46	59	64	75	76

Note: o indicates censored observations.

a. Heart transplantation and combined heart and other organ transplantation or for implantation of a cardiac mechanical assist device, are handled in the same manner as death.

Table 6. Time to Event All-Cause Mortality[a] (ITT Analysis Set)

	Pooled Tafamidis (N=264)	Placebo (N=177)
Number of all-cause mortality[a], n (%)	78 (29.5)	76 (42.9)
Number of Deaths	69 (26.1)	72 (40.7)
Number of Heart Transplants	7 (2.7)	4 (2.3)
Number of Cardiac Mechanical Assist Devices	2 (0.8)	0
Number Censored, n (%)	186 (70.5)	101 (57.1)
Reason for Censoring, n (%)		
Alive at time of analysis	186 (70.5)	101 (57.1)
Lost to Follow-up	0	0
Kaplan-Meier Estimates of Time to Event (months)		
Quartiles (95% CI)[b]		
25%	25.889 (19.844, NE)	20.928 (17.084, 22.965)
50%	NE (NE, NE)	NE (29.667, NE)
75%	NE (NE, NE)	NE (NE, NE)
Versus Placebo		
Hazard Ratio[c]	0.698	
95% CI of Hazard Ratio	(0.508, 0.958)	
p-value	0.0259	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = total number of subjects; n = number of subjects; NE = not estimable; NYHA = New York Heart Association; TTR = transthyretin.

a. Heart transplantation and combined heart and other organ transplantation or for implantation of a cardiac mechanical assist device, are handled in the same manner as death.
b. Calculated using Kaplan-Meier method
c. Hazard Ratio from a Cox Proportional Hazards model with TTR genotype (Variant and Wild-type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) in the model.

Results from analysis of the frequency of cardiovascular-related hospitalization are summarized for the ITT analysis set in Table 7. Overall, there were 138 (52.3%) and 107 (60.5%) subjects with at least 1 cardiovascular-related hospitalization in the pooled tafamidis and placebo groups, respectively. The frequency of cardiovascular-related hospitalization was 0.4750 (95% CI 0.4181, 0.5396) and 0.7025 (95% CI 0.6174, 0.7993) for the pooled tafamidis and placebo groups, respectively. The relative risk ratio between the pooled tafamidis and placebo groups was 0.6761, indicating a 32.39% reduction in the risk of cardiovascular-related hospitalization in the tafamidis group relative to placebo ($p < 0.0001$).

Table 7. Frequency of Cardiovascular-Related Hospitalizations - Pooled Active Treatment (ITT Analysis Set)

	Pooled Tafamidis (N=264)	Placebo (N=177)
Total Number of Subjects with CV-related Hospitalizations, n (%)	138 (52.3)	107 (60.5)
Frequency of CV-related Hospitalizations per Year[a]		
Mean (SD)	0.999 (2.2777)	0.884 (1.2032)
Median	0.395	0.403
Min, Max	0, 21.49	0, 7.23
Frequency of CV-related Hospitalization (95% CI)[b]	0.4750 (0.4181, 0.5396)	0.7025 (0.6174, 0.7993)
Relative Risk Ratio (Pooled Tafamidis vs Placebo) (95% CI)[b]	0.6761 (0.5639, 0.8107)	
p-value[b]	<0.0001	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; N = total number of subjects; n = number of subjects; NYHA = New York Heart Association; SD = standard deviation; TTR = transthyretin.

a. CV-related hospitalizations per year is calculated as (subject's number of CV-related hospitalizations) / (duration on study in years).

b. Poisson regression analysis with treatment, TTR Genotype (variant and wild-type), NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA baseline classification interaction terms as factors adjusted for treatment duration. Only CV-related hospitalizations where the subject is admitted to a hospital over the duration of the trial are included in this analysis; any hospitalizations prior to randomization date are not included.

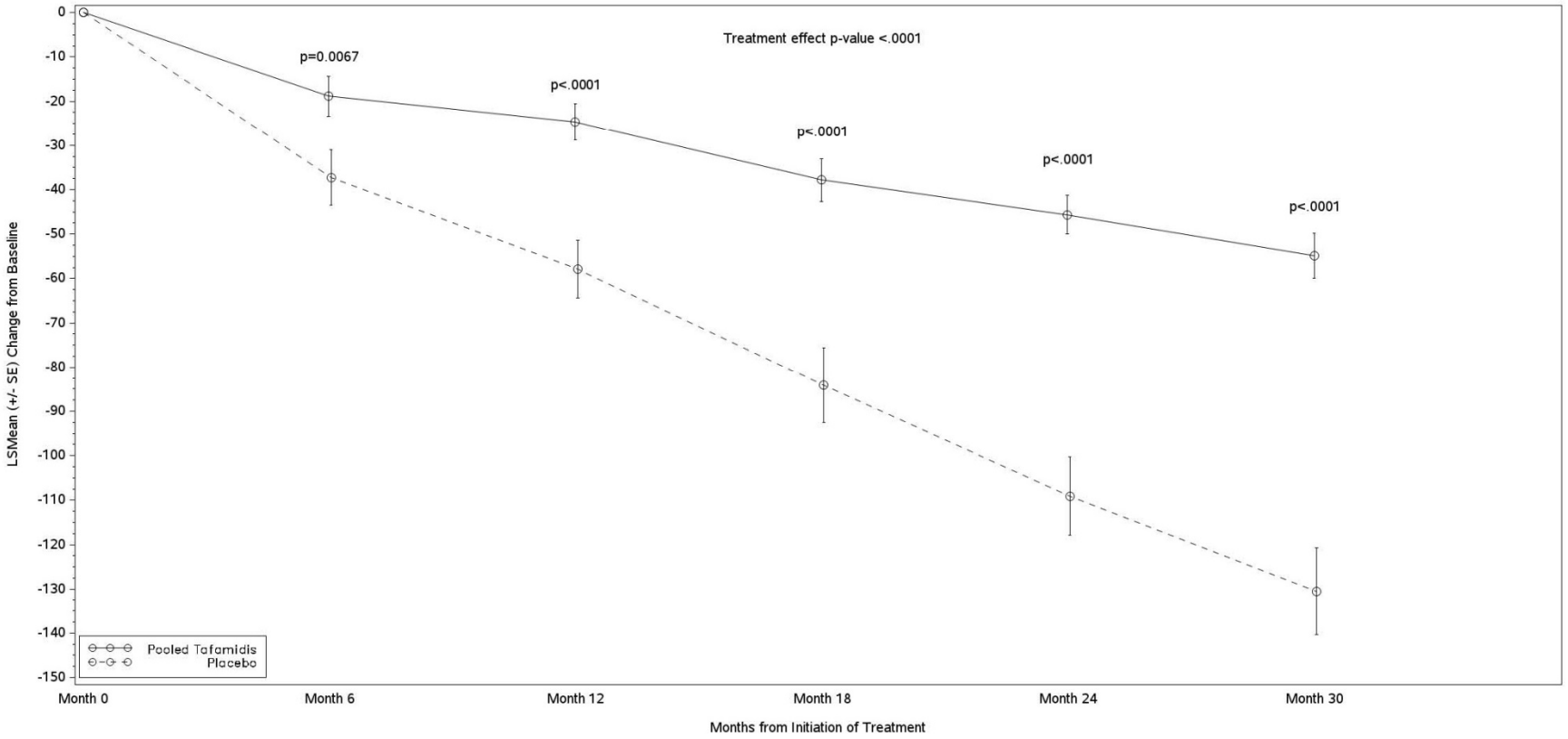
Key Secondary Analyses

Change from Baseline to Month 30 in the distance walked during the 6MWT

The pooled tafamidis LS mean change from Baseline 6MWT difference from placebo for the ITT analysis set is shown in Figure 3. A statistically significant treatment effect favoring tafamidis was observed at Month 30 (p <0.0001). The significant difference between pooled tafamidis and placebo was first observed at Month 6 (p=0.0067) and remained significant through Month 30.

Change from Baseline to Month 30 in the distance walked during the 6MWT for the pooled active treatment (ITT analysis set) is provided in Table 8. At Baseline, mean (standard deviation [SD]) 6MWT distance for the pooled tafamidis and placebo groups was 350.55 (121.296) and 353.26 (125.983) meters, respectively. At Month 30, the least squares (LS) mean (standard error [SE]) change from Baseline for the pooled tafamidis and placebo groups was -54.87 (5.068) and -130.55 (9.798) meters, respectively. The pooled tafamidis LS mean SE change from Baseline difference from placebo was 75.68 (9.236) meters (p <0.0001).

Figure 3. Distance Walked During 6-Minute Walk Test LS Means (SE) Change From Baseline to Month 30 - Pooled Active Treatment (ITT Analysis Set)



Abbreviations: ANCOVA = analysis of covariance; ITT = intent-to-treat; LS = least squares; MMRM = Mixed Model Repeated Measure; SE = standard error; TTR = transthyretin.
LS means are from an ANCOVA (MMRM) model with an unstructured covariance matrix; center and subject within center as random effects; treatment, visit, TTR genotype (variant and wild-type), and visit by treatment interaction, as fixed effects and baseline score as covariate.

Table 8. Change from Baseline to Month 30 in the Distance Walked During 6-Minute Walk Test (6MWT) - Pooled Active Treatment (ITT Analysis Set)

Visit, Units = meters	Pooled Tafamidis (N=264)	Placebo (N=177)
Baseline		
n	264	177
Mean (SD)	350.55 (121.296)	353.26 (125.983)
Median	354.00	346.00
Min, Max	24.0, 685.0	80.0, 822.0
Month 30		
n	155	70
Mean (SD)	370.44 (119.381)	333.76 (117.455)
Median	384.00	329.00
Min, Max	32.0, 634.0	60.0, 707.0
Month 30 - Change From Baseline		
n	155	70
Mean (SD)	-30.46 (87.886)	-89.67 (105.159)
Median	-23.00	-79.50
Min, Max	-377.0, 206.0	-501.0, 151.0
LS Mean (SE)	-54.87 (5.068)	-130.55 (9.798)
LS Mean (SE) Difference From Placebo	75.68 (9.236)	
95% CI of Difference	(57.56, 93.80)	
Difference p-value	<0.0001	

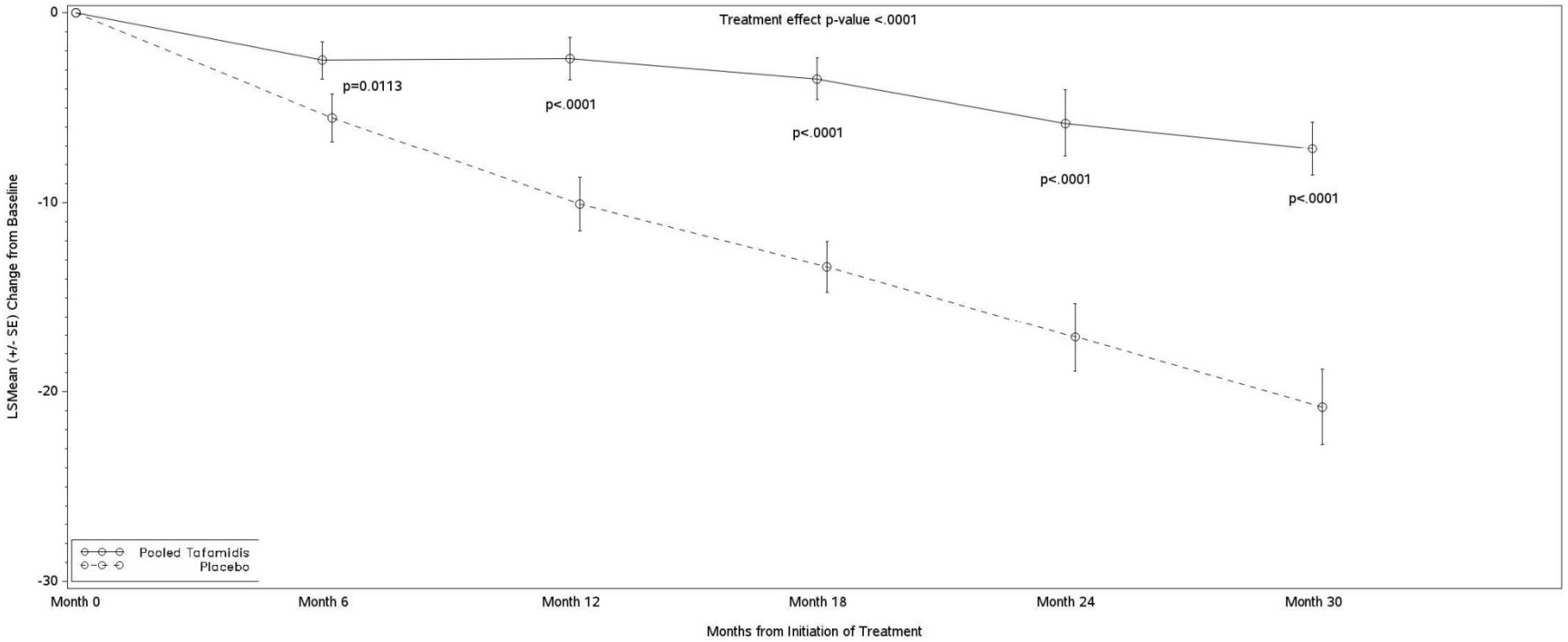
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; MMRM = Mixed Model Repeated Measure; N = total number of subjects; n = number of subjects; SD = standard deviation, SE = standard error; TTR = transthyretin.
Note: LS means are from an ANCOVA (MMRM) model with an unstructured covariance matrix (or as appropriate); center and subject within center as random effects; treatment, visit, TTR genotype (variant and wild-type), and visit by treatment interaction, as fixed effects and baseline score as covariate.

Change from Baseline to Month 30 in the KCCQ-OS Score

The pooled tafamidis LS mean change from Baseline KCCQ-OS score difference from placebo for the ITT analysis set is shown in Figure 4. A statistically significant treatment effect favoring tafamidis was observed at Month 30 (p <0.0001). The significant difference between pooled tafamidis and placebo was first observed at Month 6 (p=0.0113) and remained significant through Month 30.

Change from Baseline to Month 30 in the KCCQ-OS score for the ITT analysis set is provided in Table 9. At Baseline, mean (SD) KCCQ-OS score for the pooled tafamidis and placebo groups was 67.274 (21.3561) and 65.898 (21.7357), respectively. At Month 30, the LS mean (SE) change from Baseline for the pooled tafamidis and placebo groups was -7.16 (1.415) and -20.81 (1.971), respectively. The pooled tafamidis LS mean (SE) difference from placebo was 13.65 (2.130) (p <0.0001).

Figure 4. Kansas City Cardiomyopathy Questionnaire Overall Summary Score LS Means (SE) Change From Baseline to Month 30 - Pooled Active Treatment (ITT Analysis Set)



Abbreviations: ANCOVA = analysis of covariance; ITT = intent-to-treat; LS = least squares; MMRM = Mixed Model Repeated Measure; SE = standard error; TTR = transthyretin.

Notes: Overall Summary score is calculated as the mean of Physical Limitation, Symptom Frequency, Symptom Burden, Quality of Life, and Social Limitation Scores. LS means are from an ANCOVA (MMRM) model with an unstructured covariance matrix; center and subject within center as random effects; treatment, visit, TTR genotype (variant and wild-type), and visit by treatment interaction, as fixed effects and baseline score as covariate.

Table 9. Change From Baseline to Month 30 in the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) Score – by Pooled Active Treatment Group (ITT Analysis Set)

KCCQ-Overall Summary Score[a] Visit	Pooled Tafamidis (N=264)	Placebo (N=177)
Baseline		
n	264	177
Mean (SD)	67.274 (21.3561)	65.898 (21.7357)
Median	70.964	67.969
Min, Max	4.69, 100.00	13.80, 100.00
Month 30		
n	170	84
Mean (SD)	68.243 (21.9491)	53.829 (24.4197)
Median	71.875	51.563
Min, Max	10.16, 100.00	5.90, 100.00
Month 30 – Change from Baseline		
n	170	84
Mean (SD)	-3.855 (19.3075)	-14.637 (21.4078)
Median	-2.604	-13.281
Min, Max	-72.34, 51.30	-75.52, 33.33
LS Mean (SE)	-7.16 (1.415)	-20.81 (1.971)
LS Mean (SE) Difference From Placebo	13.65 (2.130)	
95% CI of Difference	(9.48, 17.83)	
Difference p-value	<0.0001	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; LS = least squares; max = maximum; min = minimum; MMRM = Mixed Model Repeated Measure; N = total number of subjects; n = number of subjects; SD = standard deviation, SE = standard error; TTR = transthyretin.
Note: LS means are from an ANCOVA (MMRM) model with an unstructured covariance matrix (or as appropriate); center and subject within center as random effects; treatment, visit, TTR genotype (variant and wild-type), and visit by treatment interaction, as fixed effects and baseline score as covariate.
a. Overall Summary is calculated as the mean of Physical Limitation, Symptom Frequency, Symptom Burden, Quality of Life, and Social Limitation Scores.

Secondary Analyses

Cardiovascular-Related Mortality

Results for time to event cardiovascular-related mortality for ITT analysis set are provided in Table 10. Overall, cardiovascular-related mortality for pooled tafamidis and placebo groups was 64 (24.2%) and 63 (35.6%) subjects, respectively. There were 200 (75.8%) and 114 (64.4%) subjects in the pooled tafamidis and placebo groups, respectively, who were censored. Subjects in the pooled tafamidis and placebo groups were censored because they were alive at the time of analysis (186 [70.5%] and 101 [57.1%] subjects, respectively) and deaths for all other reasons (14 [5.3%] and 13 [7.3%] subjects, respectively). The hazard ratio from the cardiovascular-related mortality Cox-proportional hazard model was 0.691 (95% CI 0.488, 0.980), indicating a 30.9% reduction in the risk of cardiovascular-related death in the pooled tafamidis group relative to the placebo group (p=0.0383).

Table 10. Time to Event Cardiovascular-Related Mortality - Pooled Active Treatment (ITT Analysis Set)

	Pooled Tafamidis (N=264)	Placebo (N=177)
Number of Cardiovascular-related events, n (%)	64 (24.2)	63 (35.6)
Cardiovascular-related Deaths[a]	55 (20.8)	59 (33.3)
Number of Heart Transplants[b]	7 (2.7)	4 (2.3)
Number of Cardiac Mechanical Assist Devices[b]	2 (0.8)	0
Number Censored, n (%)	200 (75.8)	114 (64.4)
Reason for Censoring, n (%)		
Alive at time of analysis	186 (70.5)	101 (57.1)
Deaths for all other reasons	14 (5.3)	13 (7.3)
Lost to Follow-up	0	0
Kaplan-Meier Estimates of Time to Event (months)		
Quartiles (95% CI)[c]		
25%	29.799 (23.688, NE)	22.111 (18.793, 27.105)
50%	NE (NE, NE)	NE (NE, NE)
75%	NE (NE, NE)	NE (NE, NE)
Versus Placebo		
Hazard Ratio[d]	0.691	
95% CI of Hazard Ratio	(0.488, 0.980)	
p-value	0.0383	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; NE = not estimable; N = total number of subjects; n = number of subjects; NYHA = New York Heart Association; TTR = transthyretin.

a. Deaths adjudicated as CV-related and Indeterminate.
b. Heart transplantation and combined heart and other organ transplantation or for implantation of a cardiac mechanical assist device, are handled in the same manner as death. For cardiovascular-related mortality, subjects who died for reasons other than cardiovascular (including 'indeterminate') are designated as censored at the time of death.
c. Calculated using Kaplan-Meier method
d. Hazard Ratio from a Cox Proportional Hazards model with TTR genotype (Variant and Wild-type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) in the model.

All-Cause Mortality

Pooled tafamidis results for all-cause mortality are provided above in Table 6 as supporting analyses for the primary efficacy analysis.

Frequency of Cardiovascular-Related Hospitalizations

Pooled tafamidis results for the frequency of cardiovascular-related hospitalizations are provided above in Table 7 as supporting analyses for the primary efficacy analysis.

TTR Stabilization at Month 1

TTR stabilization at Month 1 is shown for the ITT analysis set in Table 11. At Month 1 (pre-dose sample), a significantly greater proportion of subjects in the pooled tafamidis group (211/245 [86.1%] subjects) demonstrated TTR stabilization than was observed for subjects in the placebo group (6/170 [3.5%] subjects) ($p < 0.0001$). Similar results were obtained from

the sample collected which targeted the time of maximum concentration (Month 1, 4 hours 30 minutes).

Table 11. TTR Stabilization at Month 1 - Pooled Active Treatment (ITT Analysis Set)

	Pooled Tafamidis (N=264)	Placebo (N=177)
Month 1		
Number Stabilized / Number Observations	211/245 (86.1%)	6/170 (3.5%)
95% CI	81.8%, 90.5%	0.8%, 6.3%
p-value[a]	<0.0001	
Cochran Mantel Haenszel p-value	<0.0001	
Month 1 – 4 hours 30 minutes		
Number Stabilized / Number Observations	213/244 (87.3%)	6/171 (3.5%)
95% CI	83.1%, 91.5%	0.8%, 6.3%
p-value[a]	<0.0001	
Cochran Mantel Haenszel p-value	<0.0001	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; TTR = transthyretin.
Long-term stability duration was exceeded for 119 samples. Results from these samples were excluded from any summarization or analyses.
a. Based on Chi-square test for proportions.

Safety Results:

All-Causality Non-Serious Adverse Events:

All-causality non-serious treatment-emergent adverse events (TEAEs) that occurred in >5% of subjects are summarized by system organ class (SOC) and preferred term (PT) in Table 12. The most frequently reported non-serious AE by PT was fall in the tafamidis 20 mg and 80 mg treatment groups and dyspnea in the placebo group. Other frequently reported non-serious AEs by PT in all treatment groups were atrial fibrillation, fatigue, and edema peripheral.

Table 12. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term in >5% of Subjects

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Number (%) of subjects:												
Evaluable for AEs	88			176			264			177		
With AEs	85 (96.6)			159 (90.3)			244 (92.4)			168 (94.9)		
Blood and Lymphatic System Disorders	5 (5.7)	5	2	10 (5.7)	10	2	15 (5.7)	15	4	13 (7.3)	13	1
Anaemia	5 (5.7)	5	2	10 (5.7)	10	2	15 (5.7)	15	4	13 (7.3)	13	1
Cardiac disorders	30 (34.1)	59	0	49 (27.8)	75	2	79 (29.9)	134	2	62 (35.0)	127	2
Atrial fibrillation	13 (14.8)	17	0	28 (15.9)	35	0	41 (15.5)	52	0	31 (17.5)	49	0
Atrial flutter	5 (5.7)	7	0	8 (4.5)	11	0	13 (4.9)	18	0	12 (6.8)	16	1
Cardiac failure	18 (20.5)	35	0	20 (11.4)	29	2	38 (14.4)	64	2	33 (18.6)	62	1
Endocrine Disorders	5 (5.7)	6	4	12 (6.8)	12	2	17 (6.4)	18	6	10 (5.6)	10	4
Hypothyroidism	5 (5.7)	6	4	12 (6.8)	12	2	17 (6.4)	18	6	10 (5.6)	10	4
Gastrointestinal Disorders	37 (42.0)	74	8	65 (36.9)	99	38	102 (38.6)	173	46	85 (48.0)	187	45
Abdominal distension	6 (6.8)	6	2	7 (4.0)	10	5	13 (4.9)	16	7	5 (2.8)	5	2
Ascites	7 (8.0)	12	0	6 (3.4)	7	0	13 (4.9)	19	0	9 (5.1)	12	0
Constipation	14 (15.9)	15	2	25 (14.2)	25	6	39 (14.8)	40	8	30 (16.9)	36	3
Diarrhoea	10 (11.4)	11	2	22 (12.5)	25	15	32 (12.1)	36	17	39 (22.0)	52	24
Gastrooesophageal reflux disease	6 (6.8)	6	0	0	0	0	6 (2.3)	6	0	7 (4.0)	7	0
Inguinal hernia	5 (5.7)	6	0	5 (2.8)	5	0	10 (3.8)	11	0	3 (1.7)	3	0
Nausea	9 (10.2)	11	1	20 (11.4)	21	10	29 (11.0)	32	11	36 (20.3)	53	12
Vomiting	7 (8.0)	7	1	6 (3.4)	6	2	13 (4.9)	13	3	16 (9.0)	19	4
General Disorders and Administration Site Conditions	37 (42.0)	69	2	71 (40.3)	121	7	108 (40.9)	190	9	74 (41.8)	140	8
Asthenia	11 (12.5)	16	0	16 (9.1)	20	1	27 (10.2)	36	1	11 (6.2)	17	1
Fatigue	16 (18.2)	23	1	29 (16.5)	33	2	45 (17.0)	56	3	33 (18.6)	48	6
Gait disturbance	4 (4.5)	4	0	4 (2.3)	4	0	8 (3.0)	8	0	11 (6.2)	11	0
Oedema	7 (8.0)	7	0	11 (6.3)	22	0	18 (6.8)	29	0	20 (11.3)	22	0
Oedema peripheral	17 (19.3)	19	1	29 (16.5)	42	4	46 (17.4)	61	5	31 (17.5)	42	1
Infections and Infestations	31 (35.2)	51	7	73 (41.5)	111	8	104 (39.4)	162	15	72 (40.7)	114	16
Bronchitis	7 (8.0)	8	0	21 (11.9)	24	1	28 (10.6)	32	1	19 (10.7)	20	0
Cellulitis	6 (6.8)	6	0	6 (3.4)	6	2	12 (4.5)	12	2	10 (5.6)	11	0
Nasopharyngitis	7 (8.0)	9	0	14 (8.0)	17	1	21 (8.0)	26	1	17 (9.6)	23	2
Pneumonia	4 (4.5)	7	0	12 (6.8)	15	0	16 (6.1)	22	0	7 (4.0)	8	0
Sinusitis	4 (4.5)	4	0	10 (5.7)	12	0	14 (5.3)	16	0	1 (0.6)	1	0

Table 12. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term in >5% of Subjects

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Upper respiratory tract infection	7 (8.0)	7	0	17 (9.7)	19	1	24 (9.1)	26	1	16 (9.0)	18	2
Urinary tract infection	7 (8.0)	10	7	15 (8.5)	18	3	22 (8.3)	28	10	25 (14.1)	33	12
Injury, poisoning and procedural complications	27 (30.7)	42	1	43 (24.4)	64	0	70 (26.5)	106	1	40 (22.6)	75	1
Contusion	6 (6.8)	6	0	11 (6.3)	14	0	17 (6.4)	20	0	5 (2.8)	6	0
Fall	24 (27.3)	36	1	38 (21.6)	50	0	62 (23.5)	86	1	40 (22.6)	69	1
Investigations	23 (26.1)	32	5	42 (23.9)	54	10	65 (24.6)	86	15	51 (28.8)	66	12
Blood creatinine increased	3 (3.4)	4	2	9 (5.1)	9	1	12 (4.5)	13	3	8 (4.5)	8	1
Gamma-glutamyltransferase increased	3 (3.4)	3	2	9 (5.1)	9	6	12 (4.5)	12	8	11 (6.2)	11	5
International normalised ratio increased	5 (5.7)	6	1	4 (2.3)	4	1	9 (3.4)	10	2	4 (2.3)	4	0
Venous pressure jugular increased	4 (4.5)	5	0	4 (2.3)	4	0	8 (3.0)	9	0	9 (5.1)	12	0
Weight decreased	6 (6.8)	6	0	8 (4.5)	8	2	14 (5.3)	14	2	18 (10.2)	19	5
Weight increased	7 (8.0)	8	0	13 (7.4)	20	0	20 (7.6)	28	0	12 (6.8)	12	1
Metabolism and Nutrition Disorders	34 (38.6)	51	2	62 (35.2)	118	12	96 (36.4)	169	14	93 (52.5)	178	10
Decreased appetite	8 (9.1)	9	1	14 (8.0)	15	6	22 (8.3)	24	7	25 (14.1)	25	5
Fluid overload	11 (12.5)	12	0	18 (10.2)	31	1	29 (11.0)	43	1	27 (15.3)	44	1
Fluid retention	3 (3.4)	5	0	5 (2.8)	7	2	8 (3.0)	12	2	15 (8.5)	18	0
Gout	10 (11.4)	10	0	17 (9.7)	22	1	27 (10.2)	32	1	29 (16.4)	34	4
Hyperkalaemia	1 (1.1)	1	0	8 (4.5)	10	0	9 (3.4)	11	0	10 (5.6)	10	0
Hyperuricaemia	3 (3.4)	3	1	9 (5.1)	10	0	12 (4.5)	13	1	7 (4.0)	7	0
Hypokalaemia	8 (9.1)	8	0	14 (8.0)	15	1	22 (8.3)	23	1	19 (10.7)	28	0
Hyponatraemia	2 (2.3)	3	0	8 (4.5)	8	1	10 (3.8)	11	1	10 (5.6)	12	0
Musculoskeletal and Connective Tissue Disorders	32 (36.4)	55	2	71 (40.3)	124	6	103 (39.0)	179	8	70 (39.5)	133	6
Arthralgia	8 (9.1)	11	0	17 (9.7)	19	1	25 (9.5)	30	1	20 (11.3)	27	1
Back pain	9 (10.2)	9	0	17 (9.7)	18	1	26 (9.8)	27	1	23 (13.0)	29	2
Muscle spasms	10 (11.4)	13	1	15 (8.5)	15	1	25 (9.5)	28	2	14 (7.9)	19	1
Muscular weakness	2 (2.3)	2	0	5 (2.8)	8	0	7 (2.7)	10	0	12 (6.8)	12	1
Musculoskeletal pain	3 (3.4)	4	0	13 (7.4)	17	0	16 (6.1)	21	0	11 (6.2)	12	0
Myalgia	5 (5.7)	7	0	5 (2.8)	5	0	10 (3.8)	12	0	2 (1.1)	2	0
Osteoarthritis	2 (2.3)	2	0	9 (5.1)	10	0	11 (4.2)	12	0	6 (3.4)	7	0
Pain in extremity	6 (6.8)	7	1	27 (15.3)	32	3	33 (12.5)	39	4	20 (11.3)	25	1
Nervous System Disorders	28 (31.8)	46	2	52 (29.5)	76	11	80 (30.3)	122	13	59 (33.3)	91	8
Balance disorder	2 (2.3)	3	0	15 (8.5)	16	1	17 (6.4)	19	1	2 (1.1)	2	0
Carpal tunnel syndrome	5 (5.7)	5	0	4 (2.3)	4	0	9 (3.4)	9	0	4 (2.3)	6	0

Table 12. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term in >5% of Subjects

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Dizziness	16 (18.2)	20	2	25 (14.2)	31	3	41 (15.5)	51	5	32 (18.1)	36	4
Headache	1 (1.1)	1	0	9 (5.1)	11	4	10 (3.8)	12	4	11 (6.2)	13	4
Hypoaesthesia	5 (5.7)	5	0	4 (2.3)	4	0	9 (3.4)	9	0	6 (3.4)	6	0
Neuropathy peripheral	4 (4.5)	4	0	3 (1.7)	4	1	7 (2.7)	8	1	12 (6.8)	14	0
Syncope	5 (5.7)	8	0	5 (2.8)	6	2	10 (3.8)	14	2	11 (6.2)	14	0
Psychiatric Disorders	17 (19.3)	19	0	26 (14.8)	30	3	43 (16.3)	49	3	27 (15.3)	37	3
Depression	6 (6.8)	6	0	7 (4.0)	7	0	13 (4.9)	13	0	8 (4.5)	10	1
Insomnia	12 (13.6)	13	0	20 (11.4)	23	3	32 (12.1)	36	3	22 (12.4)	27	2
Renal and Urinary Disorders	16 (18.2)	27	2	28 (15.9)	36	2	44 (16.7)	63	4	43 (24.3)	55	4
Acute kidney injury	5 (5.7)	6	1	8 (4.5)	11	0	13 (4.9)	17	1	18 (10.2)	19	1
Haematuria	10 (11.4)	13	1	8 (4.5)	9	2	18 (6.8)	22	3	15 (8.5)	17	2
Renal failure	5 (5.7)	6	0	8 (4.5)	10	0	13 (4.9)	16	0	7 (4.0)	7	0
Urinary retention	2 (2.3)	2	0	6 (3.4)	6	0	8 (3.0)	8	0	12 (6.8)	12	1
Reproductive System and Breast Disorders	4 (4.5)	4	0	9 (5.1)	9	2	13 (4.9)	13	2	6 (3.4)	6	0
Gynaecomastia	4 (4.5)	4	0	9 (5.1)	9	2	13 (4.9)	13	2	6 (3.4)	6	0
Respiratory, Thoracic and Mediastinal Disorders	39 (44.3)	68	1	54 (30.7)	104	9	93 (35.2)	172	10	89 (50.3)	184	10
Cough	16 (18.2)	23	1	20 (11.4)	27	5	36 (13.6)	50	6	30 (16.9)	35	4
Dyspnoea	21 (23.9)	26	0	27 (15.3)	38	2	48 (18.2)	64	2	51 (28.8)	69	3
Dyspnoea exertional	5 (5.7)	5	0	10 (5.7)	11	1	15 (5.7)	16	1	13 (7.3)	16	0
Epistaxis	2 (2.3)	3	0	12 (6.8)	12	0	14 (5.3)	15	0	14 (7.9)	22	3
Pleural effusion	8 (9.1)	11	0	12 (6.8)	16	1	20 (7.6)	27	1	31 (17.5)	42	0
Skin and Subcutaneous Tissue Disorders	7 (8.0)	8	3	18 (10.2)	20	6	25 (9.5)	28	9	25 (14.1)	32	7
Pruritus	4 (4.5)	5	2	12 (6.8)	14	4	16 (6.1)	19	6	15 (8.5)	16	4
Rash	3 (3.4)	3	1	6 (3.4)	6	2	9 (3.4)	9	3	12 (6.8)	16	3
Vascular disorders	11 (12.5)	12	0	19 (10.8)	22	2	30 (11.4)	34	2	17 (9.6)	18	0
Hypotension	11 (12.5)	12	0	19 (10.8)	22	2	30 (11.4)	34	2	17 (9.6)	18	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; n1 = the number of occurrences of treatment emergent all causalities adverse events; n2 = the number of occurrences of treatment emergent causally related to treatment adverse events.
Notes: Except for "n1" and "n2," subjects are only counted once per treatment for each row. Includes events occurring up to 28 days after last dose of study drug. MedDRA (Version 20.1) coding dictionary applied

All-Causality Treatment-Emergent Serious Adverse Events:

The incidence of SAEs by SOC and PT are summarized in Table 13. The most frequently reported SAEs by SOC were Cardiac disorders and Infections and infestations. There were 3 SAEs in the tafamidis 20 mg group, 3 SAEs in the tafamidis 80 mg group, and 6 SAEs in the placebo group that were considered by the investigator to be treatment-related.

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Number (%) of subjects:												
Evaluable for SAEs	88			176			264			177		
With SAEs	66 (75.0)			133 (75.6)			199 (75.4)			140 (79.1)		
Blood and Lymphatic System Disorders	2 (2.3)	2	0	3 (1.7)	3	0	5 (1.9)	5	0	2 (1.1)	2	0
Anaemia	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	0	0	0
Coagulopathy	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	0	0	0
Leukocytosis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Microcytic anaemia	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Neutrophilia	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Cardiac Disorders	43 (48.9)	82	0	86 (48.9)	177	0	129 (48.9)	259	0	97 (54.8)	225	2
Acute coronary syndrome	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Acute left ventricular failure	1 (1.1)	2	0	1 (0.6)	1	0	2 (0.8)	3	0	1 (0.6)	1	0
Acute myocardial infarction	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	3 (1.7)	4	0
Angina pectoris	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Angina unstable	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Aortic valve stenosis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Arrhythmia	2 (2.3)	2	0	2 (1.1)	2	0	4 (1.5)	4	0	0	0	0
Arrhythmia supraventricular	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	1 (0.6)	1	0
Atrial fibrillation	7 (8.0)	8	0	11 (6.3)	12	0	18 (6.8)	20	0	8 (4.5)	19	0
Atrial flutter	2 (2.3)	2	0	4 (2.3)	5	0	6 (2.3)	7	0	5 (2.8)	5	0
Atrial tachycardia	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	1 (0.6)	1	0
Atrial thrombosis	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Atrioventricular block	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Atrioventricular block complete	1 (1.1)	1	0	4 (2.3)	4	0	5 (1.9)	5	0	1 (0.6)	1	0
Atrioventricular block second degree	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	1 (0.6)	1	0
Bradycardia	1 (1.1)	1	0	5 (2.8)	5	0	6 (2.3)	6	0	5 (2.8)	5	0
Cardiac amyloidosis	2 (2.3)	2	0	3 (1.7)	3	0	5 (1.9)	5	0	5 (2.8)	5	0
Cardiac arrest	1 (1.1)	1	0	2 (1.1)	2	0	3 (1.1)	3	0	6 (3.4)	6	0
Cardiac failure	16 (18.2)	25	0	34 (19.3)	50	0	50 (18.9)	75	0	39 (22.0)	61	0
Cardiac failure acute	4 (4.5)	5	0	23 (13.1)	30	0	27 (10.2)	35	0	17 (9.6)	28	0
Cardiac failure chronic	1 (1.1)	1	0	2 (1.1)	5	0	3 (1.1)	6	0	1 (0.6)	6	0
Cardiac failure congestive	15 (17.0)	17	0	20 (11.4)	31	0	35 (13.3)	48	0	32 (18.1)	46	1
Cardio-respiratory arrest	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Cardiogenic shock	3 (3.4)	3	0	2 (1.1)	2	0	5 (1.9)	5	0	4 (2.3)	5	0
Cardiomyopathy	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Cardiorenal syndrome	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Chronic left ventricular failure	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Conduction disorder	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Coronary artery disease	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	2 (1.1)	2	0
Left ventricular failure	1 (1.1)	1	0	3 (1.7)	4	0	4 (1.5)	5	0	6 (3.4)	7	0
Myocardial depression	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Myocardial infarction	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	1 (0.6)	1	0
Nodal rhythm	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Pericardial effusion	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	0	0	0
Right ventricular failure	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Sinus bradycardia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Supraventricular tachycardia	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	2 (1.1)	3	0
Systolic dysfunction	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Tachyarrhythmia	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Tachycardia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Ventricular arrhythmia	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Ventricular extrasystoles	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Ventricular fibrillation	0	0	0	0	0	0	0	0	0	3 (1.7)	3	1
Ventricular tachycardia	2 (2.3)	2	0	2 (1.1)	2	0	4 (1.5)	4	0	7 (4.0)	8	0
Congenital, Familial and Genetic Disorders	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Familial amyloidosis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Eye Disorders	0	0	0	2 (1.1)	3	0	2 (0.8)	3	0	1 (0.6)	1	0
Cataract	0	0	0	2 (1.1)	3	0	2 (0.8)	3	0	0	0	0
Conjunctival haemorrhage	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Gastrointestinal Disorders	10 (11.4)	15	2	11 (6.3)	15	1	21 (8.0)	30	3	13 (7.3)	15	0
Abdominal pain	3 (3.4)	3	0	1 (0.6)	1	0	4 (1.5)	4	0	3 (1.7)	3	0
Abdominal pain upper	0	0	0	2 (1.1)	3	0	2 (0.8)	3	0	1 (0.6)	1	0
Ascites	3 (3.4)	3	0	0	0	0	3 (1.1)	3	0	0	0	0
Colitis	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Constipation	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Diarrhoea	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Diverticulum	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Duodenitis	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Gastric haemorrhage	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Gastritis	1 (1.1)	3	2	0	0	0	1 (0.4)	3	2	0	0	0
Gastritis haemorrhagic	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Gastroduodenal ulcer	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Gastrointestinal disorder	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Gastrointestinal haemorrhage	1 (1.1)	1	0	2 (1.1)	2	0	3 (1.1)	3	0	3 (1.7)	3	0
Haematemesis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Haematochezia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Ileus	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Impaired gastric emptying	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Inguinal hernia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Melaena	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Obstructive pancreatitis	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	1 (0.6)	1	0
Oesophagitis	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Pancreatitis	0	0	0	1 (0.6)	1	1	1 (0.4)	1	1	0	0	0
Tongue disorder	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Upper gastrointestinal haemorrhage	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Vomiting	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
General Disorders and Administration Site Conditions	5 (5.7)	8	0	13 (7.4)	18	0	18 (6.8)	26	0	15 (8.5)	16	0
Asthenia	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	0	0	0
Chest discomfort	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Chest pain	2 (2.3)	3	0	4 (2.3)	5	0	6 (2.3)	8	0	2 (1.1)	2	0
Disease progression	1 (1.1)	1	0	4 (2.3)	4	0	5 (1.9)	5	0	3 (1.7)	3	0
General physical health deterioration	1 (1.1)	3	0	0	0	0	1 (0.4)	3	0	2 (1.1)	3	0
Generalised oedema	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	1 (0.6)	1	0
Incarcerated hernia	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Medical device site haematoma	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Oedema peripheral	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Peripheral swelling	0	0	0	0	0	0	0	0	0	2 (1.1)	2	0
Pyrexia	0	0	0	4 (2.3)	5	0	4 (1.5)	5	0	0	0	0
Sudden cardiac death	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Sudden death	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Hepatobiliary Disorders	1 (1.1)	1	0	3 (1.7)	3	0	4 (1.5)	4	0	3 (1.7)	3	0
Cardiac cirrhosis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Cholecystitis	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Cholecystitis acute	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Cholelithiasis	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Ischaemic hepatitis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Immune System Disorders	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	2 (1.1)	2	0
Amyloidosis	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	2 (1.1)	2	0
Infections and Infestations	19 (21.6)	24	0	32 (18.2)	38	1	51 (19.3)	62	1	37 (20.9)	43	0
Acute sinusitis	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Appendicitis	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Arthritis bacterial	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Arthritis infective	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Bacteraemia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Bacterial sepsis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Bronchitis	2 (2.3)	2	0	0	0	0	2 (0.8)	2	0	0	0	0
Cellulitis	3 (3.4)	4	0	2 (1.1)	2	0	5 (1.9)	6	0	2 (1.1)	2	0
Clostridium difficile colitis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Cystitis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Diverticulitis	0	0	0	0	0	0	0	0	0	1 (0.6)	2	0
Endocarditis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Erysipelas	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Gastroenteritis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Herpes zoster	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Infected skin ulcer	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Infectious pleural effusion	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Influenza	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	2 (1.1)	2	0
Lower respiratory tract infection	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Necrotising soft tissue infection	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Ophthalmic herpes zoster	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Osteomyelitis	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Parainfluenzae virus infection	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Pneumonia	6 (6.8)	6	0	13 (7.4)	14	0	19 (7.2)	20	0	12 (6.8)	13	0
Pneumonia legionella	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Pneumonia pneumococcal	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Pyelonephritis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Respiratory tract infection	0	0	0	0	0	0	0	0	0	2 (1.1)	2	0
Rhinitis	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Sepsis	3 (3.4)	3	0	1 (0.6)	1	0	4 (1.5)	4	0	2 (1.1)	2	0
Septic arthritis staphylococcal	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Septic shock	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	1 (0.6)	1	0
Serratia infection	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Sinusitis	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Staphylococcal bacteraemia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Staphylococcal infection	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Staphylococcal sepsis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Subcutaneous abscess	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Tonsillitis	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Tracheobronchitis	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Urinary tract infection	2 (2.3)	3	0	1 (0.6)	1	1	3 (1.1)	4	1	5 (2.8)	6	0
Urosepsis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Viral upper respiratory tract infection	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Injury, Poisoning and Procedural Complications	10 (11.4)	18	0	24 (13.6)	34	0	34 (12.9)	52	0	14 (7.9)	19	0
Concussion	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Craniocerebral injury	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Facial bones fracture	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Fall	5 (5.7)	5	0	9 (5.1)	11	0	14 (5.3)	16	0	5 (2.8)	5	0
Femoral neck fracture	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Femur fracture	1 (1.1)	1	0	2 (1.1)	2	0	3 (1.1)	3	0	0	0	0
Forearm fracture	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Head injury	0	0	0	3 (1.7)	3	0	3 (1.1)	3	0	1 (0.6)	1	0
Hip fracture	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	1 (0.6)	1	0
Injury	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Joint injury	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Laceration	2 (2.3)	2	0	1 (0.6)	1	0	3 (1.1)	3	0	0	0	0
Limb injury	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Lumbar vertebral fracture	2 (2.3)	2	0	2 (1.1)	2	0	4 (1.5)	4	0	0	0	0
Muscle rupture	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Muscle strain	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Musculoskeletal foreign body	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Overdose	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Procedural hypotension	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Procedural pain	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Rib fracture	0	0	0	3 (1.7)	3	0	3 (1.1)	3	0	0	0	0
Road traffic accident	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	1 (0.6)	1	0
Skin abrasion	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Spinal compression fracture	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Subarachnoid haemorrhage	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Subdural haematoma	0	0	0	3 (1.7)	3	0	3 (1.1)	3	0	0	0	0
Tendon rupture	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Tibia fracture	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Vasoplegia syndrome	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Wound dehiscence	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Wrist fracture	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	1 (0.6)	1	0
Investigations	3 (3.4)	3	0	5 (2.8)	5	1	8 (3.0)	8	1	4 (2.3)	4	0
Anticoagulation drug level above therapeutic	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	1 (0.6)	1	0
Anticoagulation drug level below therapeutic	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Blood potassium decreased	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Blood sodium decreased	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Ejection fraction decreased	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	0	0	0
International normalised ratio increased	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Liver function test increased	0	0	0	1 (0.6)	1	1	1 (0.4)	1	1	0	0	0
Streptococcus test positive	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Transaminases increased	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Metabolism and Nutrition Disorders	5 (5.7)	6	0	14 (8.0)	17	0	19 (7.2)	23	0	24 (13.6)	35	0
Cachexia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Dehydration	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	6 (3.4)	6	0
Diabetes mellitus	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Electrolyte imbalance	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Failure to thrive	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Fluid overload	2 (2.3)	2	0	2 (1.1)	2	0	4 (1.5)	4	0	6 (3.4)	12	0
Fluid retention	2 (2.3)	2	0	1 (0.6)	1	0	3 (1.1)	3	0	1 (0.6)	1	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Gout	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Hyperkalaemia	0	0	0	3 (1.7)	3	0	3 (1.1)	3	0	4 (2.3)	4	0
Hypoalbuminaemia	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Hypokalaemia	1 (1.1)	1	0	2 (1.1)	2	0	3 (1.1)	3	0	2 (1.1)	2	0
Hypomagnesaemia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Hyponatraemia	0	0	0	4 (2.3)	5	0	4 (1.5)	5	0	4 (2.3)	5	0
Hypovolaemia	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	1 (0.6)	1	0
Musculoskeletal and Connective Tissue Disorders	3 (3.4)	3	0	8 (4.5)	9	0	11 (4.2)	12	0	8 (4.5)	9	0
Arthralgia	0	0	0	1 (0.6)	2	0	1 (0.4)	2	0	1 (0.6)	1	0
Arthritis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Back pain	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	1 (0.6)	1	0
Gouty arthritis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Haemarthrosis	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Joint swelling	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Muscular weakness	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Neck pain	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Osteitis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Osteoarthritis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	4 (2.3)	5	0
Spondylolisthesis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Systemic lupus erythematosus	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	2 (2.3)	2	0	10 (5.7)	11	0	12 (4.5)	13	0	5 (2.8)	5	1
Adenocarcinoma	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Basal cell carcinoma	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Bladder cancer	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	0	0	0
Bladder transitional cell carcinoma	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Breast cancer	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Gallbladder adenocarcinoma	0	0	0	0	0	0	0	0	0	1 (0.6)	1	1
Intraductal papilloma of breast	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Lung neoplasm malignant	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Malignant melanoma	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Metastatic squamous cell carcinoma	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Oesophageal adenocarcinoma	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Prostate cancer	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Rectal adenoma	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Renal neoplasm	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Squamous cell carcinoma	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Testicular neoplasm	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Transitional cell carcinoma metastatic	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Nervous System Disorders	8 (9.1)	10	0	16 (9.1)	18	0	24 (9.1)	28	0	24 (13.6)	33	2
Altered state of consciousness	0	0	0	0	0	0	0	0	0	2 (1.1)	2	0
Ataxia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Carpal tunnel syndrome	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Cerebral haemorrhage	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Cerebral infarction	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Cerebrovascular accident	1 (1.1)	1	0	2 (1.1)	2	0	3 (1.1)	3	0	4 (2.3)	5	0
Cervicobrachial syndrome	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Dizziness	2 (2.3)	2	0	0	0	0	2 (0.8)	2	0	5 (2.8)	5	1
Dysarthria	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Embolic cerebral infarction	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Embolic stroke	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Epilepsy	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Haemorrhage intracranial	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Hepatic encephalopathy	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Ischaemic stroke	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Lethargy	0	0	0	0	0	0	0	0	0	1 (0.6)	1	1
Loss of consciousness	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Memory impairment	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Metabolic encephalopathy	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Neuropathy peripheral	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Presyncope	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Seizure	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Somnolence	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Syncope	0	0	0	6 (3.4)	7	0	6 (2.3)	7	0	10 (5.6)	11	0
Transient ischaemic attack	3 (3.4)	3	0	1 (0.6)	1	0	4 (1.5)	4	0	1 (0.6)	1	0
Uraemic encephalopathy	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Product Issues	0	0	0	4 (2.3)	4	0	4 (1.5)	4	0	1 (0.6)	1	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Device connection issue	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Device dislocation	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	1 (0.6)	1	0
Device malfunction	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	0	0	0
Psychiatric Disorders	0	0	0	5 (2.8)	5	0	5 (1.9)	5	0	7 (4.0)	7	0
Completed suicide	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Confusional state	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	1 (0.6)	1	0
Delirium	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Mental status changes	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	4 (2.3)	4	0
Stress	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Renal and Urinary Disorders	11 (12.5)	13	1	21 (11.9)	24	0	32 (12.1)	37	1	25 (14.1)	34	0
Acute kidney injury	9 (10.2)	10	1	13 (7.4)	14	0	22 (8.3)	24	1	15 (8.5)	22	0
Azotaemia	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Calculus urinary	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
End stage renal disease	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Haematuria	1 (1.1)	1	0	2 (1.1)	2	0	3 (1.1)	3	0	4 (2.3)	4	0
Hydronephrosis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Renal failure	1 (1.1)	1	0	2 (1.1)	2	0	3 (1.1)	3	0	3 (1.7)	3	0
Renal impairment	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	1 (0.6)	1	0
Renal injury	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Urinary bladder haemorrhage	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Urinary retention	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	1 (0.6)	1	0
Reproductive System and Breast Disorders	2 (2.3)	2	0	2 (1.1)	2	0	4 (1.5)	4	0	1 (0.6)	1	0
Benign prostatic hyperplasia	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	1 (0.6)	1	0
Cervical dysplasia	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Spermatocele	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	9 (10.2)	9	0	20 (11.4)	29	0	29 (11.0)	38	0	23 (13.0)	31	1
Acute pulmonary oedema	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Acute respiratory failure	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	4 (2.3)	5	0
Asthma	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Choking	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Chronic obstructive pulmonary disease	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	0	0	0
Cough	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Dyspnoea	2 (2.3)	2	0	3 (1.7)	3	0	5 (1.9)	5	0	4 (2.3)	4	1
Dyspnoea exertional	0	0	0	0	0	0	0	0	0	2 (1.1)	2	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Epistaxis	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	1 (0.6)	1	0
Haemoptysis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Haemothorax	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Hiccups	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Hypoxia	0	0	0	0	0	0	0	0	0	2 (1.1)	2	0
Interstitial lung disease	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Lung disorder	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Pleural effusion	5 (5.7)	5	0	6 (3.4)	8	0	11 (4.2)	13	0	4 (2.3)	6	0
Pneumonia aspiration	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Pneumonitis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Pneumothorax	0	0	0	3 (1.7)	3	0	3 (1.1)	3	0	2 (1.1)	2	0
Pulmonary embolism	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	0	0	0
Pulmonary mass	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Pulmonary oedema	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Pulmonary toxicity	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Respiratory acidosis	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Respiratory distress	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Respiratory failure	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	1 (0.6)	1	0
Skin and Subcutaneous Tissue Disorders	2 (2.3)	2	0	1 (0.6)	1	0	3 (1.1)	3	0	3 (1.7)	3	0
Dermatitis contact	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Erythema	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Neuropathic ulcer	1 (1.1)	1	0	0	0	0	1 (0.4)	1	0	0	0	0
Skin ulcer	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Stevens-Johnson syndrome	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Urticaria	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Vascular Disorders	1 (1.1)	1	0	6 (3.4)	6	0	7 (2.7)	7	0	9 (5.1)	9	0
Aortic dissection	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Circulatory collapse	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Deep vein thrombosis	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	0	0	0
Haematoma	0	0	0	2 (1.1)	2	0	2 (0.8)	2	0	0	0	0
Hypotension	1 (1.1)	1	0	1 (0.6)	1	0	2 (0.8)	2	0	2 (1.1)	2	0
Lymphoedema	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0
Orthostatic hypotension	0	0	0	1 (0.6)	1	0	1 (0.4)	1	0	2 (1.1)	2	0
Peripheral vascular disorder	0	0	0	0	0	0	0	0	0	2 (1.1)	2	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Tafamidis 20 mg n (%)	n1	n2	Tafamidis 80 mg n (%)	n1	n2	Pooled Tafamidis n (%)	n1	n2	Placebo n (%)	n1	n2
Shock haemorrhagic	0	0	0	0	0	0	0	0	0	1 (0.6)	1	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; n1 = the number of occurrences of treatment emergent all causalities adverse events; n2 = the number of occurrences of treatment emergent causally related to treatment adverse events.
Notes: Except for "n1" and "n2," subjects are only counted once per treatment for each row. Includes events occurring up to 28 days after last dose of study drug. MedDRA (Version 20.1) coding dictionary applied.

Withdrawals of Subjects from the Study

Discontinuations from the study are summarized in Table 14. A greater proportion of subjects in the placebo group (52.0%) discontinued from the study compared with the tafamidis 20 mg and 80 mg treatment groups (31.8% and 35.8%, respectively).

Table 14. Discontinuations from Study

Number (%) of Subjects	Tafamidis 20 mg N=88 n (%)	Tafamidis 80 mg N=176 n (%)	Pooled Tafamidis N=264 n (%)	Placebo N=177 n (%)
Discontinuations	28 (31.8)	63 (35.8)	91 (34.5)	92 (52.0)
Subject died[a]	14 (15.9)	25 (14.2)	39 (14.8)	38 (21.5)
Relation to study drug not defined	9 (10.2)	26 (14.8)	35 (13.3)	43 (24.3)
Protocol violation	0	1 (0.6)	1 (0.4)	1 (0.6)
Lost to follow-up	0	1 (0.6)	1 (0.4)	0
Subject no longer willing to participate in study	8 (9.1)	17 (9.7)	25 (9.5)	37 (20.9)
Other	1 (1.1)	7 (4.0)	8 (3.0)	5 (2.8)
Cardiac mechanical assist device implantation	0	2 (1.1)	2 (0.8)	0
Organ transplantation	1 (1.1)	5 (2.8)	6 (2.3)	5 (2.8)
Related to study drug[b]	0	1 (0.6)	1 (0.4)	2 (1.1)
Adverse event	0	1 (0.6)	1 (0.4)	2 (1.1)
Not related to study drug[b]	5 (5.7)	11 (6.3)	16 (6.1)	9 (5.1)
Adverse event	5 (5.7)	11 (6.3)	16 (6.1)	9 (5.1)

Abbreviations: N = total number of subjects; n = number of subjects.

a. All assessments where the relation to study drug was not defined.

b. Relationship is determined by investigator's assessment of relationship to study treatment on the adverse event case report form page.

Deaths:

A total of 144 subjects died; 77 occurred during the study period (14 [15.9%], 25 [14.2%], and 38 [21.5%] subjects in the tafamidis 20 mg, tafamidis 80 mg, and placebo groups, respectively) and 67 occurred during the follow-up period (9 [10.2%], 24 [13.6%], and 34 [19.2%] subjects in the tafamidis 20 mg, tafamidis 80 mg, and placebo groups, respectively). None of the deaths were assessed as related to treatment. The majority of deaths in the study were considered the result of underlying disease.

CONCLUSION(S):

- This Phase 3 study demonstrated the efficacy of tafamidis as therapy for subjects with TTR-CM, with statistically significant reduction at Month 30 in on all-cause mortality and the frequency of cardiovascular-related hospitalizations.

- In addition to a positive primary analysis, this study demonstrated significant and clinically meaningful effects of tafamidis on the individual components of the primary analysis (all-cause mortality and frequency of cardiovascular-related hospitalizations).

- Tafamidis treatment also significantly reduced the decline in functional capacity (6MWT) and quality of life (KCCQ-OS score). The effect of tafamidis treatment was seen at Month 6 in functional capacity (6MWT) and quality of life (KCCQ-OS score) whereas effect on overall survival emerged after approximately 18 months.

- The efficacy of tafamidis was supported by all other secondary efficacy endpoints (cardiovascular-related mortality, frequency of cardiovascular-related hospitalization, all-cause mortality, and TTR stabilization at Month 1).

- Significant treatment effects were observed for both the 20 mg and 80 mg tafamidis doses in the primary, key secondary, and secondary analyses when compared with placebo.

- Tafamidis treatment was generally safe and well tolerated in the study subject population, with few dose reductions and a similar frequency of TEAEs and serious TEAEs between the treatment groups. A greater proportion of deaths were observed in the placebo group compared with the tafamidis group. None of the deaths were related to study treatment, and most were considered as a result of the disease under study.

- The demonstrated efficacy and safety profile of tafamidis in this study population supports tafamidis as a treatment option for TTR-CM.