# CLINICAL STUDY REPORT SYNOPSIS

## SYNOPSIS

**Study Title:** A Phase 3 Multicenter, Open-Label Study to Evaluate the Safety of Daily Oral Dosing of Tafamidis Meglumine (PF-06291826-83) 20 mg or 80 mg (or Tafamidis [PF-06291826-00] 61 mg) in Subjects Diagnosed With Transthyretin Cardiomyopathy (ATTR-CM)

**Study Number:** B3461045

**Regulatory Agency or Public Disclosure Identifier Number:**

United States (US) Investigational New Drug (IND) Number: 71,880

ClinicalTrials.gov ID: NCT02791230

EudraCT Number: 2016-000868-42

**Study Phase:** Phase 3

**Name of Study Intervention:** Tafamidis (PF-06291826)

**Trade Name:** Vyndaqel / Vyndamax

**Name of Sponsor/Company:** Pfizer Inc.

**CSR Version and Report Date:** Final CSR (LPLV Date) Version 1.0, 02 May 2024

**Number of Study Centers and Investigators:**

A total of 1733 participants were enrolled at 57 centers in 17 countries/regions.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

**Publications:**

Damy T, Garcia-Pavia P, Hanna M, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. European journal of heart failure. Feb 2021;23(2):277-85.

Elliott P, Drachman BM, Gottlieb SS, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. Circulation: Heart Failure. Jan 2022;15(1):e008193.

Elliott P, Gundapaneni B, Sultan MB, et al. Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. European Journal of Heart Failure. Nov 2023;25(11):2060-4.

## CLINICAL STUDY REPORT SYNOPSIS

Elliott P, Gundapaneni B, Garcia-Pavia P. Response by Elliott et al to Letter Regarding Article: Effects of Tafamidis on Heart Failure Hospitalization: The tale of the dog that did not bark. European Journal of Heart Failure. 28 Sep 2023.

Garcia-Pavia P, Sultan MB, Gundapaneni B, et al. Tafamidis efficacy among octogenarian patients in the phase 3 ATTR-ACT and ongoing long-term extension study. Heart Failure. 1 Jan 2024;12(1):150-60.

Grogan M, Davis MK, Crespo-Leiro MG, et al. Effect of long-term tafamidis treatment on health-related quality of life in patients with transthyretin amyloid cardiomyopathy. European Journal of Heart Failure. 22 Feb 2024.

**Study Period:**

Study Initiation Date (First Participant First Visit [FPFV]): 13 June 2016

Primary Completion Date: 26 October 2023

Study Completion (Last Participant Last Visit [LPLV]) Date: 23 November 2023

This study was neither discontinued nor interrupted.

**Rationale:**

Study B3461045 was designed as a long-term extension safety study for participants completing 30 months of blinded treatment in parent Study B3461028 (Cohort A). Given the positive results of Study B3461028 and the favorable benefit-risk profile of tafamidis in transthyretin amyloid cardiomyopathy (ATTR-CM), there was justification to provide patients with an option for early access to tafamidis. Consequently, B3461045 study protocol was amended to include an additional cohort of participants with ATTR-CM who did not previously participate in parent Study B3461028 (Cohort B). The purpose of the additional cohort was to provide these patients early access to tafamidis for up to 60 months, or until local commercial availability by prescription for the ATTR-CM indication, whichever occurred earliest. Additionally, a new formulation which was bioequivalent to tafamidis meglumine 80 mg (4 × 20 mg) had been developed and was presented as tafamidis 61 mg (as the free acid). This formulation, where available, could replace the tafamidis meglumine 80 mg dose after Protocol Amendment 3.

## CLINICAL STUDY REPORT SYNOPSIS

### Objectives, Endpoints, and Statistical Methods:

| Type | Objective | Endpoints |
|---|---|---|
| **Primary** | | |
| Safety | To obtain additional, long-term, safety data for tafamidis in participants with ATTR-CM. | Safety as measured by:<br>• All-cause mortality.<br>• Incidence of treatment-emergent adverse events. |
| | To provide investigational product, tafamidis, to enrolled participants until local availability by prescription for the ATTR-CM indication. | |

For Cohort A, analyses were performed using tafamidis/tafamidis and placebo/tafamidis treatment groups. Participants randomized to tafamidis in parent Study B3461028 who continued on tafamidis in extension Study B3461045 were grouped as tafamidis/tafamidis. Participants who were randomized to placebo in parent Study B3461028 were randomized (1:2) to tafamidis 20 mg or 80 mg in extension Study B3461045 and grouped as placebo/tafamidis.

For analyses in Study B3461045 for Cohort A based on Combined Mortality Analysis Set, it combined data from participants in Study B3461028, including participants who died, discontinued in Study B3461028, or did not enroll into Study B3461045.

For Cohort B, since participants in Cohort B all administered the same dose, only overall descriptive statistics were provided.

### Methodology:

This was a Phase 3, open-label long-term extension safety study designed to obtain additional safety data for tafamidis meglumine 20 mg and 80 mg (or tafamidis 61 mg where available), and to continue to provide enrolled participants with tafamidis for up to 60 months, or until the participant had access to tafamidis by prescription for the ATTR-CM indication, whichever occurred first. The study could also end before 60 months if the sponsor discontinued the study. Participants withdrawn from the study due to commercial access to prescription tafamidis in their respective countries were considered study completers. The decision to withdraw participants for transition to commercial tafamidis was made by the sponsor.

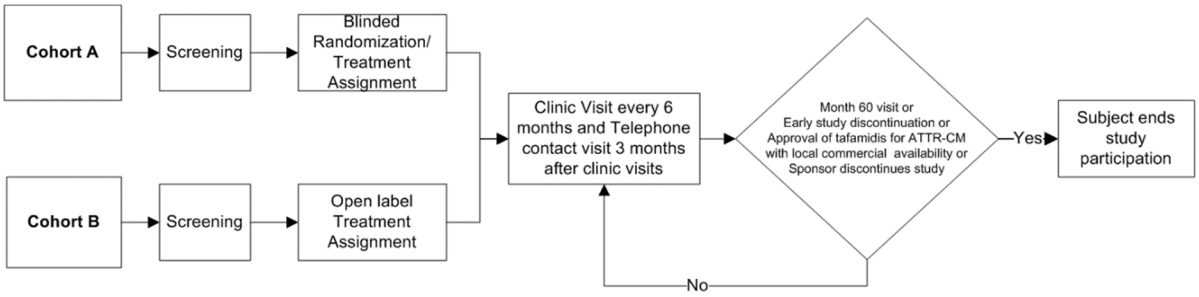
Eligible study participants were enrolled in 2 cohorts (Figure S1):

- Cohort A – Participants diagnosed with ATTR-CM who completed 30 months of participation in Study B3461028.

## CLINICAL STUDY REPORT SYNOPSIS

- Cohort B – Participants diagnosed with ATTR-CM who had not previously participated in Study B3461028.

**Figure S1. Flowchart of Study Participation**




Participants in Cohort A were assigned to open-label treatment after Protocol Amendment 3.

**Number of Participants (planned and analyzed):**

Up to 2000 participants were expected to enroll in Study B3461045.

A total of 1733 participants were enrolled (170 in the Cohort A tafamidis/tafamidis group, 82 in the Cohort A placebo/tafamidis group and 1481 in Cohort B), among whom 1728 participants were treated with tafamidis (170 in the Cohort A tafamidis/tafamidis group, 82 in the Cohort A placebo/tafamidis group and 1476 in Cohort B).

All 1728 treated participants were included in the Safety Analysis Set.

Combined Mortality Analysis Set included all 441 participants in the Intent-to-Treat Analysis Set from Study B3461028: 264 participants who received tafamidis (88 participants who received tafamidis 20 mg and 176 participants who received tafamidis 80 mg) and 177 participants who received placebo in Study B3461028.

**Diagnosis and Main Criteria for Inclusion and Exclusion:**

Participants diagnosed with ATTR-CM who completed 30 months of participation in Study B3461028 were eligible to be enrolled in Cohort A; participants (≥18 years of age) diagnosed with ATTR-CM who did not previously participate in Study B3461028 were eligible to be enrolled in Cohort B.

Participants with liver and/or heart transplant, or implanted cardiac mechanical assist device were excluded from this study.

**Study Interventions, Dose, Mode of Administration, and Batch Number(s):**

Cohort A blinded treatment: 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 plus 1 capsule of blinded tafamidis meglumine 20 mg, or 4 capsules of blinded tafamidis

## CLINICAL STUDY REPORT SYNOPSIS

meglumine 20 mg. In the event of a permanent dose reduction, the daily dose consisted of 1 capsule of blinded tafamidis meglumine 20 mg and 3 capsules of matching blinded placebo.

Cohort A and B open-label treatment: after Protocol Amendment 3, all participants were assigned to open-label treatment. Each dose of tafamidis 61 mg or tafamidis meglumine 20 mg consisted of 1 capsule. Each dose of tafamidis meglumine 80 mg consisted of 4 capsules (4 × tafamidis meglumine 20 mg). In the event of a dose reduction, the daily dose consisted of 1 capsule of tafamidis meglumine 20 mg.

The manufacturing lot numbers for the study intervention(s) dispensed in this study are provided in Table S1.

**Table S1. Study Interventions Administered**

| Investigational Product Description | Vendor Lot Number | Pfizer Lot Number | Strength/ Potency | Dosage Form |
|---|---|---|---|---|
| Placebo for Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Cap | 1514125 | 14-005784 | 0 mg | Capsule |
| Placebo for Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Cap | 3011308 | 16-001901 | 0 mg | Capsule |
| Placebo for Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Cap | 3011309 | 16-001902 | 0 mg | Capsule |
| Placebo for Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Cap | 3068389 | 16-005244 | 0 mg | Capsule |
| Placebo for Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Cap | 3138995 | 17-001908 | 0 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3143353 | 17-002147 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3143354 | 17-002148 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3386507 | 18-003180 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3386510 | 18-003183 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3386510 | 18-003184 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3386510 | 18-003324 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516662 | 18-004110 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516663 | 18-004111 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516664 | 18-004117 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516665 | 18-004118 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3386511 | 18-004121 | 61 mg | Capsule |

## CLINICAL STUDY REPORT SYNOPSIS

### Table S1. Study Interventions Administered

| Investigational Product Description | Vendor Lot Number | Pfizer Lot Number | Strength/ Potency | Dosage Form |
|---|---|---|---|---|
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3386511 | 18-004122 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3386511 | 18-004123 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516661 | 19-001054 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516662 | 19-001055 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516662 | 19-001056 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516663 | 19-001058 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516664 | 19-001059 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516664 | 19-001061 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516665 | 19-001062 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Soft Gelatin Capsule | 3516665 | 19-001063 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Unprinted SftGel Capsule | 3706046 | 19-002326 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Unprinted SftGel Capsule | P009459-0115B | 19-004417 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Unprinted SftGel Capsule | 4583678 | 21-DP-00555 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Unprinted SftGel Capsule | 4742693 | 21-DP-00809 | 61 mg | Capsule |
| Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Unprinted SftGel Capsule | 4918122 | 22-DP-01080 | 61 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 1562645 | 15-007439 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3012242 | 16-002821 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3068387 | 16-005247 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3068385 | 16-005248 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3138996 | 17-002244 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3138999 | 17-002245 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3139000 | 17-002246 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3193560 | 17-004409 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3193566 | 17-004410 | 20 mg | Capsule |

## CLINICAL STUDY REPORT SYNOPSIS

### Table S1. Study Interventions Administered

| Investigational Product Description | Vendor Lot Number | Pfizer Lot Number | Strength/ Potency | Dosage Form |
|---|---|---|---|---|
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3260993 | 18-001196 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3255966 | 18-001198 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3504086 | 19-000159 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 3787868 | 19-004103 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 4382536 | 21-DP-00414 | 20 mg | Capsule |
| Tafamidis Meglumine 20 mg Size 9.5 Oblong Yellow Soft Gelatin Unprinted Capsule | 4874447 | 22-DP-00988 | 20 mg | Capsule |

### Duration of Study Intervention:

This study was designed to provide enrolled participants with tafamidis for up to 60 months, or until participants had access to tafamidis for ATTR-CM via prescription, whichever occurred first.

### Summary of Results:

### Demographic and Other Baseline Characteristics:

The mean (standard deviation [SD]) age of the 1728 tafamidis-treated participants was 76.52 (7.60) years. There were more male participants (1542 [89.2%]) than female participants (186 [10.8%]), and most participants were White (1468 [85.0%]).

In Cohort A:

- The mean (SD) age was 76.73 (6.75) years and 76.41 (6.47) years in the tafamidis/tafamidis group and placebo/tafamidis group, respectively.
- Most participants who continued in the long-term extension study were in New York Heart Association (NYHA) functional Class II at baseline, including 122 (71.8%) participants in the tafamidis/tafamidis group and 57 (69.5%) participants in the placebo/tafamidis group.
- Most participants had the wild-type transthyretin (TTR) genotype, including 140 (82.4%) participants in the tafamidis/tafamidis group and 73 (89.0%) participants in the placebo/tafamidis group.

In Cohort B:

- The mean (SD) age was 76.51 (7.75) years.

## CLINICAL STUDY REPORT SYNOPSIS

- Most participants were in either NYHA functional Class II (781 [52.9%] participants) or NYHA functional Class III (455 [30.8%] participants) at baseline. There were 19 (1.3%) participants in NYHA functional Class IV at baseline.

- Most participants (1264 [85.6%] participants) had the wild-type TTR genotype.

The demographic characteristics are summarized below by stratification of variant TTR genotype and wild-type TTR genotype.

In Cohort A by TTR genotype:

- 30 and 9 participants had variant TTR genotype in the tafamidis/tafamidis and placebo/tafamidis groups, respectively.

  - The mean (SD) age was 73.13 (7.01) years and 71.56 (10.48) years in the tafamidis/tafamidis and placebo/tafamidis groups, respectively.

  - Most participants were male (23 [76.7%] participants in the tafamidis/tafamidis group and 6 [66.7%] participants in the placebo/tafamidis group), and most participants were White (17 [56.7%] participants in the tafamidis/tafamidis group and 6 [66.7%] participants in the placebo/tafamidis group).

  - Most participants were in NYHA functional Class II at baseline (18 [60.0%] participants in the tafamidis/tafamidis group and 8 [88.9%] participants in the placebo/tafamidis group).

- 140 and 73 participants had wild-type TTR genotype in the tafamidis/tafamidis and placebo/tafamidis groups, respectively.

  - The mean (SD) age was 77.5 (6.46) years and 77.01 (5.62) years in the tafamidis/tafamidis and placebo/tafamidis groups, respectively.

  - Most participants were male (134 [95.7%] participants in the tafamidis/tafamidis group and 68 [93.2%] participants in the placebo/tafamidis group), and most participants were White (127 [90.7%] participants in the tafamidis/tafamidis group and 66 [90.4%] participants in the placebo/tafamidis group).

  - Most participants were in NYHA functional Class II at baseline (104 [74.3%] participants in the tafamidis/tafamidis group and 49 [67.1%] participants in the placebo/tafamidis group).

In Cohort B by TTR genotype:

- Of the 212 participants with variant TTR genotype, the mean (SD) age was 70.18 (9.04) years; most participants were male (147 [69.3%] participants), and most participants were

## CLINICAL STUDY REPORT SYNOPSIS

Black or African American (112 [52.8%] participants); most participants were in NYHA functional Class II (105 [49.5%] participants) and Class III (68 [32.1%] participants) at baseline.

- Of the 1264 participants with wild-type TTR genotype, the mean (SD) age was 77.57 (6.97) years; most participants were male (1164 [92.1%] participants), and most participants were White (1189 [94.1%] participants); most participants were in NYHA functional Class II (676 [53.5%] participants) and Class III (387 [30.6%] participants) at baseline.

**Exposure:**

In the Cohort A tafamidis/tafamidis group, the mean (SD) exposure time in the long-term extension study was 848.15 (481.167) days. The mean (SD) duration of treatment was 27.78 (15.43) months.

In the Cohort A placebo/tafamidis group, the mean (SD) exposure time in the long-term extension study was 676.90 (460.460) days. The mean (SD) duration of treatment was 22.61 (14.91) months.

In Cohort B, the mean (SD) exposure time was 537.17 (418.707) days. The mean (SD) duration of treatment was 17.68 (13.82) months.

**Safety Results:**

**Incidence of Treatment-Emergent Adverse Events (TEAEs)**

- Overall Population:
    - In the Cohort A tafamidis/tafamidis group, 168 (98.8%) participants experienced 2317 TEAEs, and 19 (11.2%) participants had 32 treatment-related TEAEs. A total of 132 (77.6%) participants experienced serious adverse events (SAEs), and 1 (0.6%) participant had a treatment-related SAE.
    - In the Cohort A placebo/tafamidis group, 79 (96.3%) participants experienced 1474 TEAEs, and 19 (23.2%) participants had 30 treatment-related TEAEs. A total of 64 (78.0%) participants experienced SAEs, and 1 (1.2%) participant had a treatment-related SAE.
    - In Cohort B, 1294 (87.7%) participants experienced 8757 TEAEs, and 112 (7.6%) participants had 173 treatment-related TEAEs. A total of 736 (49.9%) participants experienced SAEs, and 9 (0.6%) participants had treatment-related SAEs.

## CLINICAL STUDY REPORT SYNOPSIS

- Participants With Variant TTR Genotype:
    - In the Cohort A tafamidis/tafamidis group, 29 (96.7%) participants experienced 242 TEAEs, and 3 (10.0%) participants had 5 treatment-related TEAEs. A total of 23 (76.7%) participants experienced SAEs; none of these SAEs were considered treatment-related by the investigator.
    - In the Cohort A placebo/tafamidis group, 8 (88.9%) participants experienced 91 TEAEs, and 2 (22.2%) participants had 2 treatment-related TEAEs. A total of 5 (55.6%) participants experienced SAEs; none of these SAEs were considered treatment-related by the investigator.
    - In Cohort B, 184 (86.8%) participants experienced 1197 TEAEs, and 14 (6.6%) participants had 31 treatment-related TEAEs. A total of 100 (47.2%) participants experienced SAEs; none of these SAEs were considered treatment-related by the investigator.
- Participants With Wild-Type TTR Genotype:
    - In the Cohort A tafamidis/tafamidis group, 139 (99.3%) participants experienced 2075 TEAEs, and 16 (11.4%) participants had 27 treatment-related TEAEs. A total of 109 (77.9%) participants experienced SAEs, and 1 (0.7%) participant had a treatment-related SAE.
    - In the Cohort A placebo/tafamidis group, 71 (97.3%) participants experienced 1383 TEAEs, and 17 (23.3%) participants had 28 treatment-related TEAEs. A total of 59 (80.8%) participants experienced SAEs, and 1 (1.4%) participant had a treatment-related SAE.
    - In Cohort B, 1110 (87.8%) participants experienced 7560 TEAEs, and 98 (7.8%) participants had 142 treatment-related TEAEs. A total of 636 (50.3%) participants experienced SAEs, and 9 (0.7%) participants had treatment-related SAEs.

**Incidence of All-Causality TEAEs:**

In the Cohort A tafamidis/tafamidis group, 10 (5.9%) participants had mild TEAEs, 46 (27.1%) participants had moderate TEAEs and 112 (65.9%) participants had severe TEAEs. The most frequently reported TEAEs were Fall (41 [24.1%] participants), Atrial fibrillation (32 [18.8%] participants) and Dyspnoea (31 [18.2%] participants).

In the Cohort A placebo/tafamidis group, 3 (3.7%) participants had mild TEAEs, 19 (23.2%) participants had moderate TEAEs and 57 (69.5%) participants had severe TEAEs. The most frequently reported TEAEs were Fall (34 [41.5%] participants), Pleural effusion (24 [29.3%] participants) and Hypotension (20 [24.4%] participants).

## CLINICAL STUDY REPORT SYNOPSIS

In Cohort B, 273 (18.5%) participants had mild TEAEs, 465 (31.5%) participants had moderate TEAEs and 556 (37.7%) participants had severe TEAEs. The most frequently reported TEAEs were Cardiac failure (167 [11.3%] participants), Atrial fibrillation (150 [10.2%] participants) and Fall (146 [9.9%] participants).

**Incidence of Treatment-Related TEAEs:**

Overall Population:

- In the Cohort A tafamidis/tafamidis group, 11 (6.5%) participants had mild treatment-related TEAEs, 6 (3.5%) participants had moderate treatment-related TEAEs and 2 (1.2%) participants had severe treatment-related TEAEs. All treatment-related TEAEs were reported in single participants except Diarrhoea (reported in 3 [1.8%] participants) and Constipation (reported in 2 [1.2%] participants).

- In the Cohort A placebo/tafamidis group, 9 (11.0%) participants had mild treatment-related TEAEs, 9 (11.0%) participants had moderate treatment-related TEAEs and 1 (1.2%) participant had a severe treatment-related TEAE. The most frequently reported treatment-related TEAEs were Gamma-glutamyltransferase increased (5 [6.1%] participants) and Pruritus (3 [3.7%] participants), and all other treatment-related TEAEs were reported in 1 or 2 participants.

- In Cohort B, 58 (3.9%) participants had mild treatment-related TEAEs, 50 (3.4%) participants had moderate treatment-related TEAEs and 4 (0.3%) participants had severe treatment-related TEAEs. The most frequently reported treatment-related TEAEs were Diarrhoea (26 [1.8%] participants) and Fatigue (10 [0.7%] participants).

Participants With Variant TTR Genotype:

- In the Cohort A tafamidis/tafamidis group, a total of 5 treatment-related TEAEs occurred in 3 (10.0%) participants (Hypothyroidism, Constipation, Gait disturbance, Culture urine positive, Dry skin) and each was reported in single participant.

- In the Cohort A placebo/tafamidis group, a total of 2 (22.2%) participants experienced 2 treatment-related TEAEs of Oesophageal candidiasis and Liver function test abnormal (each event was reported in single participant).

- In Cohort B, all treatment-related TEAEs were reported in single participants except Diarrhoea (reported in 3 [1.4%] participants), Nausea, Decreased appetite and Urinary tract infection (reported in 2 [0.9%] participants each).

## CLINICAL STUDY REPORT SYNOPSIS

Participants With Wild-Type TTR Genotype:

- In the Cohort A tafamidis/tafamidis group, all treatment-related TEAEs were reported in single participants except Diarrhoea (3 [2.1%] participants).
- In the Cohort A placebo/tafamidis group, the most frequently reported treatment-related TEAEs were Gamma-glutamyltransferase increased (5 [6.8%] participants) and Pruritus (3 [4.1%] participants), and all other treatment-related TEAEs were reported in 1 or 2 participants.
- In Cohort B, the most frequently reported treatment-related TEAEs were Diarrhoea (23 [1.8%] participants) and Fatigue (10 [0.8%] participants).

**Discontinuations From Study Due to Adverse Events (AEs)**

- Overall Population:
  - In the Cohort A tafamidis/tafamidis group, 23 (13.5%) participants experienced TEAEs leading to discontinuation from study, and all these TEAEs were reported in single participants except Cardiac failure reported in 3 (1.8%) participants. None of these TEAEs leading to permanent discontinuation from study were considered related to treatment by the investigator.
  - In the Cohort A placebo/tafamidis group, 14 (17.1%) participants experienced TEAEs leading to discontinuation from study, and all these TEAEs were reported in single participants except Cardiac failure, Cardiac failure congestive and Underdose (all reported in 2 [2.4%] participants each). None of these TEAEs leading to permanent discontinuation from study were considered related to treatment by the investigator.
  - In Cohort B, 106 (7.2%) participants experienced TEAEs leading to discontinuation from study, with the most common TEAE being Cardiac failure (13 [0.9%] participants). A total of 9 (0.6%) participants discontinued from study due to treatment-related TEAEs.
- Variant TTR Genotype:
  - In the Cohort A tafamidis/tafamidis group, 2 (6.7%) participants experienced TEAEs of Myocardial infarction and Generalised oedema (each reported in 1 [3.3%] participant) leading to discontinuation from study. None of these TEAEs leading to permanent discontinuation from study were considered related to treatment by the investigator.
  - No participant in the Cohort A placebo/tafamidis group had TEAEs leading to discontinuation from study.

## CLINICAL STUDY REPORT SYNOPSIS

- In Cohort B, 17 (8.0%) participants experienced TEAEs leading to discontinuation from study, and all these TEAEs were reported in single participants except Sudden death and Dyspnoea (each reported in 2 [0.9%] participants). A total of 2 (0.9%) participants discontinued from study due to treatment-related TEAEs.

- Wild-Type TTR Genotype:

  - In the Cohort A tafamidis/tafamidis group, 21 (15.0%) participants experienced TEAEs leading to discontinuation from study, and all these TEAEs were reported in single participants except Cardiac failure reported in 3 (2.1%) participants. None of these TEAEs leading to permanent discontinuation from study were considered related to treatment by the investigator.

  - In the Cohort A placebo/tafamidis group, 14 (19.2%) participants experienced TEAEs leading to discontinuation from study, and all these TEAEs were reported in single participants except Cardiac failure, Cardiac failure congestive and Underdose (all reported in 2 [2.7%] participants each). None of these TEAEs leading to permanent discontinuation from study were considered related to treatment by the investigator.

  - In Cohort B, 89 (7.0%) participants experienced TEAEs leading to discontinuation from study, with the most common TEAE being Cardiac failure (12 [0.9%] participants). A total of 7 (0.6%) participants discontinued from study due to treatment-related TEAEs.

**Discontinuations From Study Intervention Due to AEs**

- Overall Population:

  - In the Cohort A tafamidis/tafamidis group, 20 (11.8%) participants experienced TEAEs leading to discontinuation from treatment, and all of these TEAEs were reported in single participants except Cardiac failure, Cardiac failure congestive and Dysphagia (all reported in 2 [1.2%] participants each).

  - In the Cohort A placebo/tafamidis group, 14 (17.1%) participants experienced TEAEs leading to discontinuation from treatment, and all of these TEAEs were reported in single participants except Cardiac failure (reported in 2 [2.4%] participants) and Cardiac failure congestive (reported in 4 [4.9%] participants).

  - In Cohort B, 100 (6.8%) participants experienced TEAEs leading to discontinuation from treatment, with the most common TEAE being Cardiac failure (15 [1.0%] participants).

  - No participant in this study discontinued study drug due to treatment-related TEAEs but continued in the study.

## CLINICAL STUDY REPORT SYNOPSIS

- Variant TTR Genotype:
    - In the Cohort A tafamidis/tafamidis group, 3 (10.0%) participants experienced TEAEs of Cardiac failure, Myocardial infarction and Generalised oedema (each reported in 1 participant) leading to discontinuation from treatment.
    - In the Cohort A placebo/tafamidis group, 2 (22.2%) participants experienced TEAEs of Cardiac failure and Renal impairment (each reported in 1 participant) leading to discontinuation from treatment.
    - In Cohort B, 15 (7.1%) participants experienced TEAEs leading to discontinuation from treatment, and all these TEAEs were reported in single participants except Dyspnoea reported in 2 (0.9%) participants.
- Wild-Type TTR Genotype:
    - In the Cohort A tafamidis/tafamidis group, 17 (12.1%) participants experienced TEAEs leading to discontinuation from treatment, and all these TEAEs were reported in single participants except Cardiac failure congestive and Dysphagia reported in 2 (1.4%) participants each.
    - In the Cohort A placebo/tafamidis group, 12 (16.4%) participants experienced TEAEs leading to discontinuation from treatment, and all these TEAEs were reported in single participants except Cardiac failure congestive (reported in 4 [5.5%] participants).
    - In Cohort B, 85 (6.7%) participants experienced TEAEs leading to discontinuation from treatment, with the most common TEAE being Cardiac failure (14 [1.1%] participants).

**Temporary Discontinuations Due to AEs**

- Overall Population:
    - In the Cohort A tafamidis/tafamidis group, 22 (12.9%) participants experienced TEAEs leading to temporary treatment discontinuation, and all these TEAEs were reported in single participants except Cardiac failure, Cardiac failure congestive, Vomiting and Fall (all reported in 2 [1.2%] participants each). There was 1 (0.6%) participant with temporary discontinuation due to treatment-related TEAEs.
    - In the Cohort A placebo/tafamidis group, 11 (13.4%) participants experienced TEAEs leading to temporary treatment discontinuation, and all these TEAEs were reported in single participants. A total of 3 (3.7%) participants had temporary discontinuations due to treatment-related TEAEs.

## CLINICAL STUDY REPORT SYNOPSIS

- In Cohort B, 83 (5.6%) participants experienced TEAEs leading to temporary treatment discontinuation, with the most common TEAEs being Fatigue (7 [0.5%] participants) and Cardiac failure (6 [0.4%] participants). A total of 18 (1.2%) participants had temporary discontinuations due to treatment-related TEAEs.

- Variant TTR Genotype:

  - In the Cohort A tafamidis/tafamidis group, 7 (23.3%) participants experienced TEAEs leading to temporary treatment discontinuation, and all these TEAEs were reported in single participants. There was 1 (3.3%) participant with temporary discontinuation due to treatment-related TEAEs.

  - In the Cohort A placebo/tafamidis group, 4 (44.4%) participants experienced TEAEs leading to temporary treatment discontinuation, and all these TEAEs were reported in single participants. There was 1 (11.1%) participant with temporary discontinuation due to treatment-related TEAE.

  - In Cohort B, 9 (4.2%) participants experienced TEAEs leading to temporary treatment discontinuation, and all these TEAEs were reported in single participants except Cardiac failure, Dysphagia and Nausea (all reported in 2 [0.9%] participants each). A total of 3 (1.4%) participants had temporary discontinuations due to treatment-related TEAEs.

- Wild-Type TTR Genotype:

  - In the Cohort A tafamidis/tafamidis group, 15 (10.7%) participants experienced TEAEs leading to temporary treatment discontinuation, and all these TEAEs were reported in single participants except Cardiac failure, Cardiac failure congestive, Vomiting and Fall (all reported in 2 [1.4%] participants each). None of these TEAEs were considered related to treatment by the investigator.

  - In the Cohort A placebo/tafamidis group, 7 (9.6%) participants experienced TEAEs leading to temporary treatment discontinuation, and all these TEAEs were reported in single participants. A total of 2 (2.7%) participants had temporary discontinuations due to treatment-related TEAEs.

  - In Cohort B, 74 (5.9%) participants experienced TEAEs leading to temporary treatment discontinuation, with the most common TEAE being Fatigue (7 [0.6%] participants). A total of 15 (1.2%) participants had temporary discontinuations due to treatment-related TEAEs.

## CLINICAL STUDY REPORT SYNOPSIS

### Dose Reductions Due to AEs

- Overall Population:
    - In the Cohort A tafamidis/tafamidis group, 2 (1.2%) participants experienced TEAEs leading to dose reduction, and all these TEAEs were reported in single participants. There was 1 (0.6%) participant with treatment-related TEAEs leading to dose reduction.
    - In the Cohort A placebo/tafamidis group, 1 (1.2%) participant experienced a TEAE of Abdominal pain leading to dose reduction, and this TEAE was not related to treatment as assessed by the investigator.
    - In Cohort B, 8 (0.5%) participants experienced TEAEs leading to dose reduction, and all these TEAEs were reported in single participants except Diarrhoea (reported in 5 [0.3%] participants). A total of 5 (0.3%) participants had treatment-related TEAEs leading to dose reduction.
- Variant TTR Genotype:
    - In the Cohort A tafamidis/tafamidis group, 1 (3.3%) participant experienced a TEAE of Feeling abnormal leading to dose reduction, and this TEAE was not related to treatment as assessed by the investigator.
    - In the Cohort A placebo/tafamidis group, no participant had TEAE leading to dose reduction.
    - In Cohort B, 1 (0.5%) participant experienced a TEAE of Diarrhoea leading to dose reduction, and this TEAE was considered related to treatment by the investigator.
- Wild-Type TTR Genotype:
    - In the Cohort A tafamidis/tafamidis group, 1 (0.7%) participant experienced TEAEs of Breath odour, Diarrhoea, Dizziness, Headache, Dyspnoea, Pruritus and Skin odour abnormal which led to the dose reduction. All these TEAEs were considered related to treatment by the investigator.
    - In the Cohort A placebo/tafamidis group, 1 (1.4%) participant experienced a TEAE of Abdominal pain leading to dose reduction, and this TEAE was not related to treatment as assessed by the investigator.
    - In Cohort B, 7 (0.6%) participants experienced TEAEs leading to dose reduction, and all of these TEAEs were reported in single participants except Diarrhoea (reported in 4 [0.3%] participants). A total of 4 (0.3%) participants had treatment-related TEAEs leading to dose reduction.

## CLINICAL STUDY REPORT SYNOPSIS

### All-Causality SAEs

- Overall Population:
    - The most frequently reported SAE was Cardiac failure in Cohort A tafamidis/tafamidis group (30 [17.6%] participants), Cohort A placebo/tafamidis group (17 [20.7%] participants) and Cohort B (169 [11.4%] participants).
- Variant TTR Genotype:
    - In the Cohort A tafamidis/tafamidis group, the most frequently reported SAE was Cardiac failure (6 [20.0%] participants).
    - In the Cohort A placebo/tafamidis group, all SAEs were reported in single participants except Cardiac failure (2 [22.2%] participants) and Cardiac failure congestive (3 [33.3%] participants).
    - In Cohort B, the most frequently reported SAE was Cardiac failure (17 [8.0%] participants).
- Wild-Type TTR Genotype:
    - The most frequently reported SAE was Cardiac failure in Cohort A tafamidis/tafamidis group (24 [17.1%] participants), Cohort A placebo/tafamidis group (15 [20.5%] participants) and Cohort B (152 [12.0%] participants).

### Treatment-Related SAEs

- Overall Population:
    - 1 (0.6%) participant in the Cohort A tafamidis/tafamidis group had a treatment-related SAE of Cardiac arrest.
    - 1 (1.2%) participant in the Cohort A placebo/tafamidis group had a treatment-related SAE of Constipation.
    - 9 (0.6%) participants in Cohort B had treatment-related SAEs, which were all reported in single participants except Fatigue (reported in 2 [0.1%] participants).
    - All participants with treatment-related SAEs had wild-type TTR genotype.
- No participant with variant TTR genotype had treatment-related SAEs.

## CLINICAL STUDY REPORT SYNOPSIS

### Discontinuations From Study Due to SAEs

- Overall Population:
    - In the Cohort A tafamidis/tafamidis group, 20 (11.8%) participants experienced SAEs leading to discontinuation from study, and all these SAEs were reported in single participants except Cardiac failure reported in 3 (1.8%) participants.
    - In the Cohort A placebo/tafamidis group, 11 (13.4%) participants experienced SAEs leading to discontinuation from study, and all these SAEs were reported in single participants except Cardiac failure and Cardiac failure congestive reported in 2 (2.4%) participants each.
    - In Cohort B, 85 (5.8%) participants experienced SAEs leading to discontinuation from study, with the most common SAE being Cardiac failure (12 [0.8%] participants).
- Variant TTR Genotype:
    - In the Cohort A tafamidis/tafamidis group, 2 (6.7%) participants experienced SAEs of Myocardial infarction and Generalised oedema (either reported in 1 participant) leading to discontinuation from study.
    - No participant in the Cohort A placebo/tafamidis group had an SAE leading to discontinuation from study.
    - In Cohort B, 13 (6.1%) participants experienced SAEs leading to discontinuation from study, and all these SAEs were reported in single participants except Sudden death reported in 2 (0.9%) participants.
- Wild-Type TTR Genotype:
    - In the Cohort A tafamidis/tafamidis group, 18 (12.9%) participants experienced SAEs leading to discontinuation from study, and all these SAEs were reported in single participants except Cardiac failure reported in 3 (2.1%) participants.
    - In the Cohort A placebo/tafamidis group, 11 (15.1%) participants experienced SAEs leading to discontinuation from study, and all these SAEs were reported in single participants except Cardiac failure and Cardiac failure congestive reported in 2 (2.7%) participants each.
    - In Cohort B, 72 (5.7%) participants experienced SAEs leading to discontinuation from study, with the most common SAE being Cardiac failure (11 [0.9%] participants).

## CLINICAL STUDY REPORT SYNOPSIS

**Deaths**

A total of 451 (26.1%) participants died in the Safety Analysis Set, among whom 247 (14.3%) died during the Study B3461045 period.

- In the Cohort A tafamidis/tafamidis group, 38 (22.4%) participants died during the Study B3461045 period, and 27 (15.9%) participants died after the study period (defined as up to 60 months from study enrollment). Most deaths were considered due to disease under study (34 participants).

- In the Cohort A placebo/tafamidis group, 25 (30.5%) participants died during the Study B3461045 period, and 23 (28.0%) participants died after the study period (defined as up to 60 months from study enrollment). Most deaths were considered due to disease under study (32 participants).

- In Cohort B, 184 (12.5%) participants died during the Study B3461045 period, and 154 (10.4%) participants died after the study period (defined as up to 60 months from study enrollment). Most deaths were due to disease under study (147 participants).

**All-Cause Mortality of Cohort A (Combined Mortality Analysis Set)**

All-cause mortality included deaths, heart transplants and cardiac mechanical assist devices implantation treated as death. All-cause mortality of Cohort A participants in the Combined Mortality Analysis Set is summarized below.

- Overall Population:

    - Among 264 participants in the Cohort A tafamidis/tafamidis group, 132 (50.0%) participants died, 10 (3.8%) participants underwent heart transplants, and 2 (0.8%) participants underwent implantation of cardiac mechanical assist devices. Kaplan-Meier estimate of the median time to all-cause mortality events was 58.7 (95% confidence interval [CI]: 50.3, 68.4) months.

    - Among 177 participants in the Cohort A placebo/tafamidis group, 120 (67.8%) participants died, 6 (3.4%) participants underwent heart transplants, and no participant underwent implantation of cardiac mechanical assist device. Kaplan-Meier estimate of the median time to all-cause mortality events was 35.8 (95% CI: 29.7, 41.1) months.

    - The hazard ratio from the time to events obtained from the Cox-proportional hazards model for the Cohort A tafamidis/tafamidis group was 0.6202 (95% CI: 0.4865, 0.7906), indicating a 37.98% reduction in the risk of all-cause mortality events in participants treated with continuous tafamidis relative to the participants who received placebo followed by tafamidis (p-value = 0.0001).

## CLINICAL STUDY REPORT SYNOPSIS

- Variant TTR Genotype:
    - Among 63 participants in the Cohort A tafamidis/tafamidis group, 37 (58.7%) participants died, 5 (7.9%) participants underwent heart transplants, and 2 (3.2%) participants underwent implantation of cardiac mechanical assist devices. Kaplan-Meier estimate of the median time to all-cause mortality events was 34.6 (95% CI: 21.3, 48.7) months.
    - Among 43 participants in the Cohort A placebo/tafamidis group, 31 (72.1%) participants died, 1 (2.3%) participant underwent heart transplant, and no participant underwent implantation of cardiac mechanical assist device. Kaplan-Meier estimate of the median time to all-cause mortality events was 23.5 (95% CI: 16.9, 30.6) months.
    - The hazard ratio from the time to events obtained from the Cox-proportional hazards model for the Cohort A tafamidis/tafamidis group was 0.6698 (95% CI: 0.4175, 1.0747), indicating a 33.02% reduction in the risk of all-cause mortality events in participants treated with continuous tafamidis relative to the participants who received placebo followed by tafamidis (p-value = 0.0967).
- Wild-Type TTR Genotype:
    - Among 201 participants in the Cohort A tafamidis/tafamidis group, 95 (47.3%) participants died, 5 (2.5%) participants underwent heart transplants, and no participant underwent implantation of cardiac mechanical assist device. Kaplan-Meier estimate of the median time to all-cause mortality events was 67.6 (95% CI: 54.4, 79.9) months.
    - Among 134 participants in the Cohort A placebo/tafamidis group, 89 (66.4%) participants died, 5 (3.7%) participants underwent heart transplants, and no participant underwent implantation of cardiac mechanical assist device. Kaplan-Meier estimate of the median time to all-cause mortality events was 38.6 (95% CI: 34.1, 47.1) months.
    - The hazard ratio from the time to events obtained from the Cox-proportional hazards model for the Cohort A tafamidis/tafamidis group was 0.5749 (95% CI: 0.4312, 0.7666), indicating a 42.51% reduction in the risk of all-cause mortality events in participants treated with continuous tafamidis relative to the participants who received placebo followed by tafamidis (p-value = 0.0002).

All-cause mortality (deaths only) of Cohort A participants in the Combined Mortality Analysis Set is summarized below.

## CLINICAL STUDY REPORT SYNOPSIS

- Overall Population:
    - Among 264 participants in the Cohort A tafamidis/tafamidis group, 137 (51.9%) participants died. Kaplan-Meier estimate of the median time to death was 62.6 (95% CI: 51.3, 70.2) months.
    - Among 177 participants in the Cohort A placebo/tafamidis group, 120 (67.8%) participants died. Kaplan-Meier estimate of the median time to death was 36.9 (95% CI: 31.2, 43.3) months.
    - The hazard ratio from the time to events obtained from the Cox-proportional hazards model for the Cohort A tafamidis/tafamidis group was 0.6136 (95% CI: 0.4786, 0.7868), indicating a 38.64% reduction in the risk of death in participants treated with continuous tafamidis relative to the participants who received placebo followed by tafamidis (p-value = 0.0001).
- Variant TTR Genotype:
    - Among 63 participants in the Cohort A tafamidis/tafamidis group, 41 (65.1%) participants died. Kaplan-Meier estimate of the median time to death was 38.6 (95% CI: 26.1, 51.8) months.
    - Among 43 participants in the Cohort A placebo/tafamidis group, 31 (72.1%) participants died. Kaplan-Meier estimate of the median time to death was 24.5 (95% CI: 19.1, 31.2) months.
    - The hazard ratio from the time to events obtained from the Cox-proportional hazards model for the Cohort A tafamidis/tafamidis group was 0.59 (95% CI: 0.3623, 0.9608), indicating a 41% reduction in the risk of death in participants treated with continuous tafamidis relative to the participants who received placebo followed by tafamidis (p-value = 0.0339).
- Wild-Type TTR Genotype:
    - Among 201 participants in the Cohort A tafamidis/tafamidis group, 96 (47.8%) participants died. Kaplan-Meier estimate of the median time to death was 68.4 (95% CI: 55.3, 80.8) months.
    - Among 134 participants in the Cohort A placebo/tafamidis group, 89 (66.4%) participants died. Kaplan-Meier estimate of the median time to death was 41.7 (95% CI: 35.8, 50.7) months.
    - The hazard ratio from the time to events obtained from the Cox-proportional hazards model for the Cohort A tafamidis/tafamidis group was 0.5837 (95% CI: 0.4347, 0.7836), indicating a 41.63% reduction in the risk of death in participants treated with

## CLINICAL STUDY REPORT SYNOPSIS

continuous tafamidis relative to the participants who received placebo followed by tafamidis (p-value = 0.0003).

**All-Cause Mortality of Cohort B**

All-cause mortality included deaths, heart transplants and cardiac mechanical assist devices implantation treated as death.

- In the overall population of Cohort B, 336 (22.8%) participants died, 7 (0.5%) participants underwent heart transplants, and 2 (0.1%) participants underwent implantation of cardiac mechanical assist devices.

- In the variant TTR genotype participants of Cohort B, 40 (18.9%) participants died, 1 (0.5%) participant underwent heart transplant, and no participant underwent implantation of cardiac mechanical assist device.

- In the wild-type TTR genotype participants of Cohort B, 296 (23.4%) participants died, 6 (0.5%) participants underwent heart transplants, and 2 (0.2%) participants underwent implantation of cardiac mechanical assist devices.

**Conclusions:**

**Primary Endpoints:**

- In Cohort A, based on the pivotal data from Study B3461028 combined with the long-term extension Study B3461045, there was a significantly greater survival benefit with continuous tafamidis, which further emphasized the importance of prompt diagnosis and treatment initiation. Most deaths during the Study B3461045 period were considered to be due to the disease under study.

- In Cohort B, most deaths were due to the disease under study, and survival rates were aligned with life expectancy in this population.

- Tafamidis was well tolerated with a favorable safety profile.

- The incidence of treatment-related TEAEs was numerically higher in the Cohort A placebo/tafamidis group (23.2%) than that in the Cohort A tafamidis/tafamidis group (11.2%). Treatment-related TEAEs were generally mild to moderate in severity.

- No participant discontinued study drug due to treatment-related TEAEs but continued in the study. Dose reductions due to treatment-related TEAEs occurred in less than 1% of participants in this study.

- No new safety signals were identified in this study.