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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Vyndaqel® / Tafamidis meglumine

PROTOCOL NO.: Fx-006 (B3461021)

PROTOCOL TITLE: An Open-Label Extension of Study Fx-005 Evaluating Long-Term Safety and Clinical Outcomes of Fx-1006A in Patients with Transthyretin Amyloid Polyneuropathy

Study Centers: A total of 7 centers participated in study including 2 centers in Portugal and one each in Argentina, Brazil, France, Germany, and Sweden.

Study Initiation and Final Completion Dates: 25 July 2008 to 28 October 2010

Phase of Development: Phase 2/3

Study Objectives:

- Evaluate the long-term safety and tolerability of chronic administration of tafamidis (Fx-1006A) in subjects with transthyretin amyloidosis polyneuropathy (ATTR-PN)
- Evaluate the long-term effects of tafamidis on disease progression in subjects with ATTR-PN
- Determine the pharmacodynamic (PD) stabilization effect of tafamidis on human valine replaced by methionine at position 30 (V30M) transthyretin (TTR)
- Obtain additional pharmacokinetic (PK) samples for population PK analysis in this subject population

METHODS

Study Design: This was an international, multicenter, single treatment arm study designed to determine the long-term safety and tolerability of tafamidis as well as the effects of tafamidis on clinical outcomes in subjects with ATTR-PN. Subjects who completed the Month 18 visit of a previous study (Safety and Efficacy of Orally Administered Fx-1006A in Patients With Familial Amyloid Polyneuropathy [FAP]: A Randomized, Double-blind, Placebo-controlled Study; NCT00409175) were eligible to enroll in this open-label extension study. Subjects received once-daily oral 20 mg tafamidis for 12 months (former placebo subjects in previous study were crossed over to active drug). It was intended that there be no interruption in study medication administration between the 2 studies. However, 2 South

American sites and 1 site in Portugal (Lisbon) experienced an extended interval between the end of the previous study and the initiation of the extension study (due to a delay in regulatory approval). The schedule of events is presented in Table 1.

Table 1. Schedule of Events

Procedure	Baseline[a]	Treatment Period				
		Day 1	6 Wk Visit ±2 Days	3 Mo Visit ±1 Wk	6 Mo Visit ±2 Wk	12 Mo Visit ±2 Wks
Informed consent	X					
Review of entrance criteria	X					
Enrollment	X					
Medical history/demographics	X					
Norfolk QOL-DN	X				X	X
Nerve conduction studies	X				X	X
NIS-LL[b]	X				X	X
Physical examination	X					X
Abbreviated physical examination			X	X	X	
Body weight	X				X	X
Body height	X					
Vital signs	X		X	X	X	X
12-Lead ECG	X		X	X	X	X
Quantitative Sensory Testing (CASE IV)	X				X	X
Heart rate response to deep breathing	X				X	X
Urine pregnancy test (females of child-bearing potential only)	X		X	X	X	X
Laboratory tests[c]	X		X	X	X	X
Blood sample for PK analysis	X		X		X	X
Blood sample for TTR stabilization assay	X		X		X	X
Echocardiography	X				X	X
Holter monitoring[d]	X				X	X
Eye examination (including fundal photography)	X				X	X
Skin biopsy for IENF[e]	X					
Study medication compliance			X	X	X	X
Study medication dispensation	X		X	X	X	
First study medication dose		X				
Adverse events[f]	X	X	X	X	X	X
Concomitant medications[f]	X	X	X	X	X	X

CASE IV = Computer Aided Sensory Evaluator, Version 4; ECG = electrocardiogram; IENF = intraepidermal nerve fiber; Mo = months; NIS-LL= Neuropathy Impairment Score – Lower Limb; NT-pro-BNP = N-terminal pro-hormone natriuretic peptide; PK = pharmacokinetics; QOL-DN = Quality of Life – Diabetic Neuropathy; TTR = transthyretin; Wk = week.

a. Month 18 of the previous study (or the start of Study Fx-006 in subjects with >2 months interruption between the previous study and Fx-006).

b. NIS-LL testing was performed 2 times at least 24 hours apart within a 1-week period at Baseline. Both evaluations were completed prior to study drug administration. All NIS-LL testing for a particular subject was performed twice, at least 24 hours apart within 1 week by the same Neurologist throughout the course of the study.

c. Serum chemistry (including troponin I and NT-pro-BNP), coagulation panel, hematology, and urinalysis.

Table 1. Schedule of Events

d.	Holter monitoring for the baseline assessment were conducted at either Month 18 visit of the previous study at which NIS-LL testing was conducted.
e.	Skin biopsies for the baseline assessment of IENF were conducted at either Month 18 visit of the previous study at which NIS-LL testing was conducted. Skin biopsies were required per-protocol for all subjects except those at Site 1 (Porto, Portugal). In these subjects, skin biopsies were optional.
f.	Monthly telephone contact (±1 week of the scheduled date) to monitor for adverse events and concurrent medications including a final telephone contact 1 month after the last dose of study drug. All subjects were contacted 30 days after the last dose of study drug to assess adverse events and concomitant medication use.

Number of Subjects (Planned and Analyzed): It was anticipated that approximately 100 subjects were to complete the previous study and enroll in this open-label extension. A total of 86 subjects were enrolled (57 in Portugal, 7 each in Sweden and Argentina, 6 each in Brazil and Germany, 3 in France), 85 were dosed, and 77 completed 12 months of treatment.

Diagnosis and Main Criteria for Inclusion: Male and non-pregnant female subjects who completed the Month 18 visit of the previous study were eligible. All subjects provided written informed consent and were, in the Investigator's opinion, willing and able to comply with the study medication regimen and all other study requirements.

Study Treatment: All subjects received a once-daily oral dose of 20-mg tafamidis in a soft gelatin capsule formulation for 12 months; subjects randomized to placebo in the previous study crossed over to active drug (tafamidis 20 mg); subjects were instructed to self-administer study medication at home once daily, at the same time each day, orally with water and without regard for food intake, for 12 months.

Tafamidis meglumine was supplied in 10-count child resistant blister packs as 12 capsules filled with a suspension containing 20 mg of tafamidis meglumine. The only active ingredient in tafamidis meglumine was tafamidis. The dose of tafamidis administered to subjects in this open-label extension study (20 mg once daily) was the same as that used in the previous study.

Efficacy and Safety Endpoints:

Efficacy Endpoints:

- Response to treatment at Months 6 and 12, as indicated by either improvement (decrease from Baseline) or stabilization (change from Baseline of 0 to <2) in the Neurologic Impairment Score – Lower Limb (NIS-LL) score. The NIS-LL score for each study visit was based on the average of 2 scores taken at least 24 hours apart within a 1 week period
- Rate of Progression and Change from Baseline to Months 6 and 12 in the Total Quality of Life (TQOL) score, as measured by the Norfolk QOL-Diabetic Neuropathy (DN)
- Change from Baseline to Months 6 and 12 in NIS-LL
- Change from Baseline to Months 6 and 12 in the five domains of the Norfolk QOL-DN

- Change from Baseline to Months 6 and 12 in sum 7 composite score" as measured by nerve conduction studies, vibration detection threshold (VDT) and heart rate response to deep breathing

- Change from Baseline to Months 6 and 12 in heat, pain and cooling thresholds as measured by Quantitative Sensory Testing utilizing CASE IV

- Rate of Disease Progression and Change from Baseline to Months 6 and 12 in modified Body Mass Index (mBMI)

- Change from Baseline to Months 6 and 12 in intraepidermal nerve fiber density (IENF)

- Change from Baseline to Week 6 and Months 3, 6, and 12 in troponin I and N terminal pro-hormone natriuretic peptide (NT-pro-BNP) levels

- Comparison of IENF density at Baseline between those treated with tafamidis in previous study and those treated with placebo in previous study. In addition, the correlation of IENF density with other measures of neurologic impairment.

- IENF density at Baseline

- TTR stabilization at Months 6 and 12, as measured by a validated immunoturbidimetric assay

Safety Endpoints:

- Incidence of subjects experiencing treatment-emergent serious adverse events (SAEs)

- Incidence of subjects experiencing treatment-emergent ≥ Grade 3 adverse events (AEs)

- Incidence of subjects with treatment-emergent echocardiography (ECHO) findings considered by the Investigator to be clinically significant

- Incidence of subjects with treatment-emergent electrocardiogram (ECG) findings considered by the Investigator to be clinically significant.

- Incidence of subjects with treatment-emergent Holter Monitor findings considered by the Investigator to be clinically significant.

- Incidence of subjects discontinuing from the study due to AEs

Safety Evaluations: The assessment of safety was performed on and is presented for the safety population. This evaluation has taken into account recorded AEs, clinical laboratory testing, vital signs, ECG (including Holter monitoring) and ECHO assessments, physical and eye examinations, and the use of concomitant medications.

Statistical Methods: Four analysis populations were pre-specified in the statistical analysis plan:

Safety population: all subjects who received at least 1 dose of study medication. Safety analyses were performed using this population.

Intent-to-treat (ITT) population: all subjects who received at least 1 dose of study medication and had no more than 2 months interruption between the previous study and Fx-006. All efficacy assessments were performed using this population.

Efficacy evaluable population: ITT subjects who had non-missing Month 12 NIS-LL and TQOL scores, received at least 80% of study medication, and had no major protocol violations that could materially impact the efficacy assessments. In addition to the ITT population, all efficacy assessments were performed in this population.

Treatment interruption population: subjects who received at least 1 dose of study medication and had more than 2 months study medication interruption between the previous study and Fx-006.

The following hypotheses were tested (groups are identified by the treatment sequence subjects received in the previous study and Study Fx-006):

- Sustainability of the treatment effect in slowing disease progression in subjects treated with tafamidis for 30 months (tafamidis-tafamidis group): compare the rate of disease progression as measured by the monthly rate of change (or slope) of the various endpoints during the last 12 months of treatment (during Study Fx-006) with the rate of change during the first 18 months of treatment (during the previous study) for the tafamidis-tafamidis group.

- Superiority of the treatment effect in slowing disease progression in subjects treated with tafamidis for 12 months (placebo-tafamidis group): compare the rate of disease progression during 12 months of tafamidis treatment (during Study Fx-006) with the previous rate of change during 18 months of placebo treatment (during the previous study) for the placebo-tafamidis group. Superiority of the treatment effect in slowing disease progression in subjects treated with tafamidis for 12 months only.

- In order to evaluate whether early initiation of treatment (early-start treatment effect) exhibits long-lasting effects in slowing disease progression, the change from Baseline to the Fx-006 Month 12 assessment was evaluated for each endpoint and compared between the tafamidis-tafamidis group and the placebo-tafamidis group.

Data from the previous study (Baseline and Months 6, 12, and 18) and Fx-006 (Baseline and Months 6 and 12) were analyzed using a mixed model analysis of variance to assess the sustainability and superiority of the treatment effect. The dependent variable was the measurement at different visits. The independent variables were the study by treatment interaction, and the time-by-study-by-treatment interaction. The intercept and time variables were modeled as random effects. The test of treatment effect was based on the time by study by treatment interaction. If each subject had the same number of observations, this model

would be equivalent to the following two-stage analysis. First, estimate the slope of each subject's measurements by linear regression for the previous study and Fx-006 separately and second, compare the slopes using a paired t-test between the previous study and Fx-006.

The use of a mixed model is an improvement to this analysis in the case where all subjects do not have the same number of measurements. The analysis optimally weights each subject's slope by a function of its precision. No imputation was applied for mixed models.

The change from the previous study Baseline to Fx-006 Month 12 by treatment sequence group was compared using a t-test or Wilcoxon rank sum test to assess the early-start treatment effect. The previous study Baseline was used as covariate by analysis of covariance.

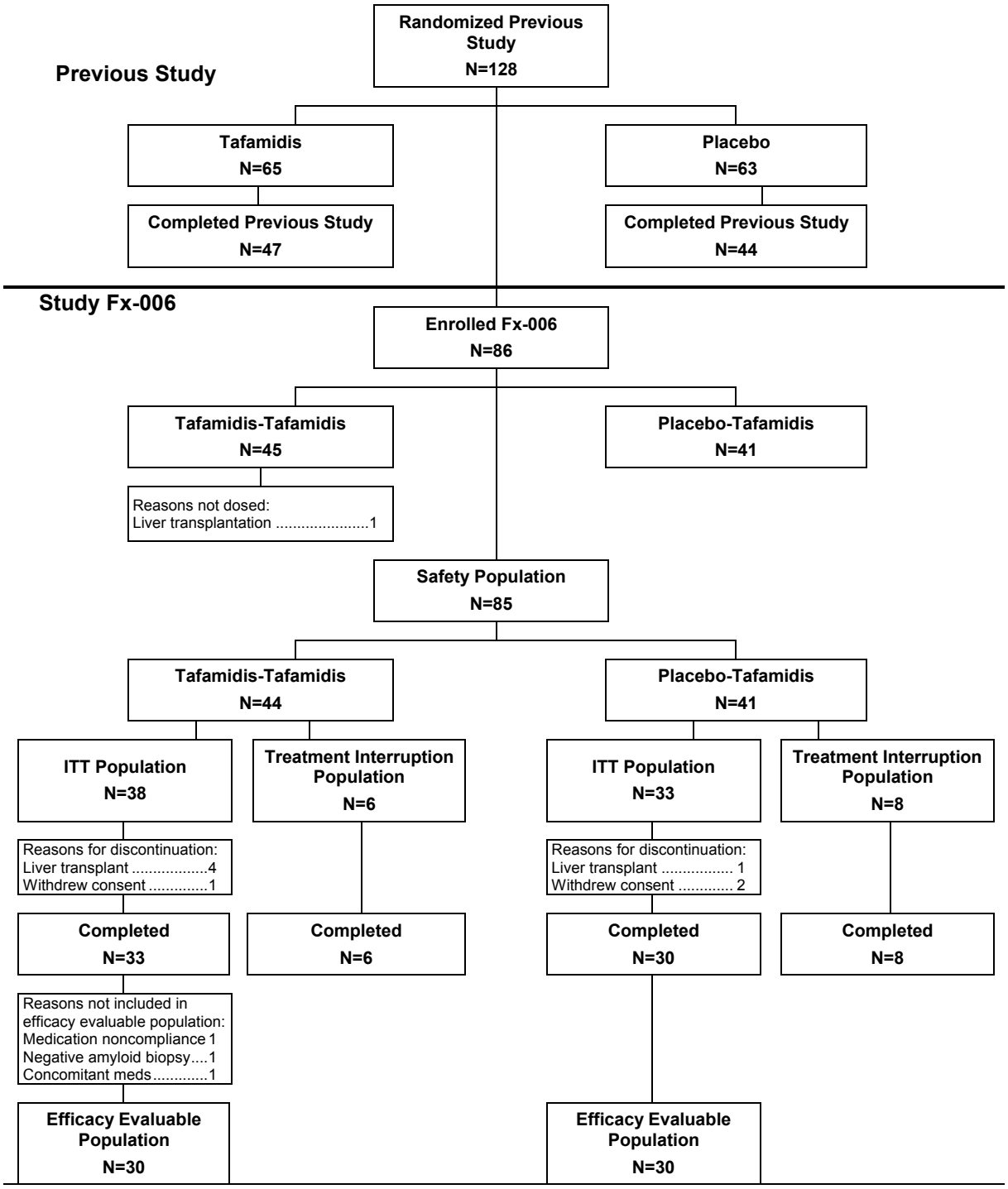
The proportion of subjects with the NIS-LL response to treatment (as defined by a change in NIS-LL score of <2) and 95% confidence intervals (CI) were summarized by treatment sequence group and visit.

Pharmacodynamics Analysis: TTR stabilization was measured at Week 6, and at Months 6 and 12. The proportion of subjects achieving TTR stabilization and 95% CI were summarized at each time point.

RESULTS

Subject Disposition and Demography: A total of 86 subjects were enrolled (45 in the tafamidis-tafamidis group and 41 in the placebo-tafamidis group). A total of 85 subjects were dosed (one subject discontinued prior to dosing due to liver transplant) and comprised the safety population. There were 71 subjects in the ITT population (38 in the tafamidis-tafamidis group and 33 in the placebo-tafamidis group), and 14 subjects in the treatment interruption population (6 and 8 subjects in the respective treatment sequence groups; Figure 1).

Figure 1. Subject Disposition and Analysis Populations (Study Fx-006)



N = total number of subjects.

A summary of demographics for the safety population is presented in Table 2.

Table 2. Demographics – Safety Population

Variable	Tafamidis-Tafamidis N=44	Placebo-Tafamidis N=41	All Subjects N=85	p-Value[a]
Age				
Mean (SD)	41.3 (13.41)	39.6 (13.18)	40.4 (13.25)	0.3811
Median	36.5	36.0	36.0	
Range	26, 76	24, 73	24, 76	
Age group, n (%)				
≤65 years	38 (86.4)	38 (92.7)	76 (89.4)	0.4858
>65 years	6 (13.6)	3 (7.3)	9 (10.6)	
Gender, n (%)				
Female	24 (54.5)	23 (56.1)	47 (55.3)	1.0000
Race, n (%)				
Caucasian	38 (86.4)	37 (90.2)	75 (88.2)	1.0000
Latino	5 (11.4)	4 (9.8)	9 (10.6)	
Not available	1 (2.3)	0	1 (1.2)	
Height, cm				
Mean (SD)	166.1 (11.01)	166.5 (10.74)[b]	166.3 (10.82)	0.7605
Median	163	168.5	164.25	
Range	147, 186	149, 188	147, 188	
Duration of symptoms, months				
Mean (SD)	62.8 (52.30)	53.6 (34.32)	58.4 (44.52)	0.7649
Median	41.8	39.7	40.1	
Range	21, 287	20, 152	20, 287	

Demographics are the previous study Month 18 values (Fx-006 Baseline).
N = total number of subjects; n = number of subjects with prespecified criteria; SD = standard deviation.
a. p-Values are based on Wilcoxon's rank sum test for continuous variables and Fisher's Exact test for categorical variables.
b. For placebo-tafamidis height, n=40.

Efficacy, Pharmacokinetic, Pharmacodynamic Results: One of the objectives of this study was to evaluate the longer-term efficacy of tafamidis on disease progression over 30 months of treatment. This was accomplished by comparing the rate of change in the last 12 months with the first 18 months of treatment, the overall rate of change over the full 30 months of treatment, and the mean changes from the previous study baseline at each assessment time point in the tafamidis-tafamidis treatment sequence group.

Sustainability: The endpoints evaluated included the NIS-LL, Norfolk QOL-DN (TQOL), large (Summated 7-nerve tests–normal deviates [Σ7 NTs nds]) and small (Summated 3-nerve tests–small-fiber normal deviates [Σ3 NTSF nds]) nerve fiber function, clinical/neurophysiological function composite endpoints (NIS-LL+Σ7 and NIS-LL+Σ3), and mBMI. The results are presented for the ITT population in Table 3.

Table 3. Sustainability of the Treatment Effect: Rate of Change per Month for all Efficacy Endpoints – ITT Population

Endpoint	Rate of Change in U/month (SEM)				
	Tafamidis-Tafamidis (N=38)				Placebo (N=61)
	Fx-006 (12 Months)	Previous Study 18 Months[a]	p-Value[b]	Previous Study/ Fx-006 (30 Months[c])	Previous Study 18 Months[a, d]
NIS-LL	0.11 (0.07)	0.08 (0.06)	0.6000	0.10 (0.04)	0.34 (0.05)
Norfolk QOL-DN (TQOL)	0.25 (0.20)	-0.03 (0.15)	0.1632	0.04 (0.07)	0.46 (0.15)
Σ7 NTs nds	0.05 (0.05)	0.06 (0.03)	0.9298	0.06 (0.02)	0.18 (0.03)
Σ3 NTSF nds	0.05 (0.02)	0.03 (0.02)	0.3348	0.03 (0.01)	0.09 (0.02)
NIS-LL+Σ7	0.17 (0.09)	0.13 (0.06)	0.6881	0.15 (0.04)	0.54 (0.07)
NIS-LL+Σ3	0.15 (0.07)	0.11 (0.06)	0.5635	0.12 (0.03)	0.44 (0.05)
mBMI	-2.00 (1.04)	1.85 (0.73)	0.0006	0.37 (0.44)	-1.62 (0.62)

ANOVA = analysis of variance; ITT = intent-to-treat; mBMI = modified body mass index; NIS-LL = Neuropathy Impairment Score – Lower Limb; Σ3 NTSF nds = summated 3-nerve tests–small-fiber normal deviates; Σ7 NTs nds = summated 7-nerve tests–normal deviates; OQL-DN = Quality of Life – Diabetic Neuropathy; TQOL = total quality of life score.

a. Results of the previous study.
b. p-Values (comparing the rate of change for the tafamidis-tafamidis group in Study Fx-006 to the rate of change in the previous study) based on a mixed model ANOVA. The dependent variable was the measurement at each visit. The independent variables were the study-by-treatment interaction and the time-by-study-by-treatment interaction. The intercept and time variables were modeled as random effects. The test of treatment effect was based on the time-by-study-by-treatment interaction.
c. Results of the previous study/Fx-006 at 30 months.
d. ITT subjects treated with placebo in the previous study.

The sustainability of the tafamidis treatment effect was also determined in the efficacy evaluable population. This population of subjects was identified to assess whether subjects who completed 12 months of tafamidis treatment with no significant protocol violations had outcomes that differed from the ITT population. The results are presented in Table 4.

Table 4. Sustainability of the Treatment Effect: Rate of Change per Month for all Efficacy Endpoints – Efficacy Evaluable Population (Study Fx-006)

Endpoint	Rate of Change in U/month (SEM)				
	Tafamidis-Tafamidis (N=30)				Placebo (N=42)
	Fx-006 (12 months)	Previous Study (18 Months)[a]	p-Value[b]	Previous Study/Fx-006 (30 Months)[c]	Previous Study (18 months)[a, d]
NIS-LL	0.07 (0.08)	0.06 (0.06)	0.9638	0.07 (0.04)	0.33 (0.06)
Norfolk QOL-DN (TQOL)	0.13 (0.21)	-0.19 (0.16)	0.1275	-0.08 (0.06)	0.45 (0.17)
Σ7 NTs nds	0.05 (0.05)	0.05 (0.04)	0.9943	0.05 (0.02)	0.17 (0.04)
Σ3 NTSF nds	0.05 (0.03)	0.03 (0.02)	0.3896	0.03 (0.01)	0.09 (0.02)
NIS-LL+Σ7	0.12 (0.09)	0.11 (0.07)	0.9726	0.12 (0.05)	0.50 (0.07)
NIS-LL+Σ3	0.09 (0.08)	0.09 (0.06)	0.9945	0.09 (0.03)	0.42 (0.06)
mBMI	-1.88 (1.10)	1.95 (0.81)	0.0014	0.40 (0.45)	-1.27 (0.67)

ANOVA = analysis of variance; ITT = intent-to-treat; mBMI = modified body mass index; NIS-LL = Neuropathy Impairment Score – Lower Limb; Σ3 NTSF nds = summated 3-nerve tests–small-fiber normal deviates; Σ7 NTs nds = summated 7-nerve tests–normal deviates; OQL-DN = Quality of Life – Diabetic Neuropathy; SEM = standard error of mean; TQOL = total quality of life score.

a. Results of the previous study.
b. p-Values (comparing the rate of change for the tafamidis-tafamidis group in Study Fx-006 to the rate of change in the previous study) based on a mixed model ANOVA. The dependent variable was the measurement at each visit. The independent variables were the study-by-treatment interaction and the time-by-study-by-treatment interaction. The intercept and time variables were modeled as random effects. The test of treatment effect was based on the time-by-study-by-treatment interaction.
c. Results of the previous study/Fx-006 at 30 months.
d. Efficacy evaluable subjects treated with placebo in the previous study.

Rate of Disease Progression: The superiority of the treatment effect was assessed by comparing the rate of disease progression (as measured by the monthly rate of change or slope) for each endpoint during the last 12 months of treatment (i.e., Study Fx-006) with the first 18 months of treatment (i.e., the previous study) in the placebo-tafamidis group.

To place these results into perspective, the rate of disease progression of the 64 subjects who received tafamidis in the previous study is also provided.

The endpoints evaluated included the NIS-LL, Norfolk QOL-DN (TQOL), large (Σ7 NTs nds) and small (Σ3 NTSF nds) nerve fiber function, clinical/neurophysiological function composite endpoints (NIS-LL+Σ7 and NIS-LL+Σ3), and mBMI. The results are presented for the ITT population in Table 5.

Table 5. Superiority of the Treatment Effect: Rate of Change per Month for all Efficacy Endpoints – ITT Population (Study Fx-006)

Endpoint	Rate of Change in U/month (SEM)			
	Placebo-Tafamidis (N=33)			Tafamidis (N=64)
	Fx-006 (12 Months)	Previous Study (18 Months)[a]	p-Value[b]	Previous Study (18 Months)[a,]
NIS-LL	0.16 (0.08)	0.34 (0.06)	0.0103	0.16 (0.05)
Norfolk QOL-DN (TQOL)	-0.16 (0.21)	0.61 (0.16)	0.0003	0.12 (0.15)
Σ7 NTs nds	0.11 (0.05)	0.18 (0.04)	0.2133	0.08 (0.03)
Σ3 NTSF nds	0.04 (0.03)	0.09 (0.02)	0.0551	0.02 (0.02)
NIS-LL+Σ7	0.26 (0.10)	0.52 (0.07)	0.0055	0.25 (0.07)
NIS-LL+Σ3	0.20 (0.08)	0.43 (0.06)	0.0016	0.17 (0.05)
mBMI	5.19 (1.13)	-1.77 (0.78)	<0.0001	2.05 (0.61)

ANOVA = analysis of variance; Number of ITT subjects in the placebo-tafamidis group =33.
ITT = intent-to-treat; mBMI = modified body mass index; NIS-LL = Neuropathy Impairment Score – Lower Limb; Σ3 NTSF nds = summated 3-nerve tests–small-fiber normal deviates; Σ7 NTs nds = summated 7-nerve tests–normal deviates; OQL-DN = Quality of Life – Diabetic Neuropathy; SEM = standard error of mean; TQOL = total quality of life score.

a. Results of the previous study.
b. p-Values (comparing the rate of change in the placebo-tafamidis group in Study Fx-006 to the rate of change in the previous study) based on a mixed model ANOVA. The dependent variable was the measurement at each visit. The independent variables were the study-by-treatment interaction and the time-by-study-by-treatment interaction. The intercept and time variables were modeled as random effects. The test of treatment effect was based on the time-by-study-by-treatment interaction.
c. ITT subjects treated with tafamidis in the previous study.

The superiority of the tafamidis treatment effect was also determined in the efficacy evaluable population. The results are presented in Table 6. The slowing of disease progression observed in subjects previously treated with placebo in the previous study who completed 12 months of tafamidis in Study Fx-006 (i.e., efficacy evaluable subjects in the placebo-tafamidis treatment sequence group) was similar to the ITT population.

Table 6. Superiority of the Treatment Effect: Rate of Change per Month for all Efficacy Endpoints – Efficacy Evaluable Population (Study Fx-006)

Endpoint	Rate of Change in U/month (SEM)			
	Placebo-Tafamidis (N=30)			Tafamidis (N=45)
	Fx-006 (12 Months)	Previous Study (18 Months)[a]	p-Value[b]	Previous Study (18 Months)[c]
NIS-LL	0.14 (0.08)	0.31 (0.06)	0.0253	0.09 (0.06)
Norfolk QOL-DN (TQOL)	-0.18 (0.21)	0.56 (0.16)	0.0006	0.07 (0.17)
Σ7 NTs nds	0.11 (0.05)	0.18 (0.04)	0.2461	0.07 (0.04)
Σ3 NTSF nds	0.04 (0.03)	0.09 (0.02)	0.0438	0.02 (0.02)
NIS-LL+Σ7	0.25 (0.09)	0.49 (0.07)	0.0145	0.16 (0.07)
NIS-LL+Σ3	0.17 (0.08)	0.40 (0.06)	0.0037	0.11 (0.06)
mBMI	5.26 (1.13)	-1.87 (0.81)	<0.0001	1.89 (0.65)

ANOVA = analysis of variance; ITT = intent-to-treat; mBMI = modified body mass index; NIS-LL = Neuropathy Impairment Score – Lower Limb; Σ3 NTSF nds = summated 3-nerve tests–small-fiber normal deviates; Σ7 NTs nds = summated 7-nerve tests–normal deviates; OQL-DN = Quality of Life – Diabetic Neuropathy; SEM = standard error of mean; TQOL = total quality of life score.

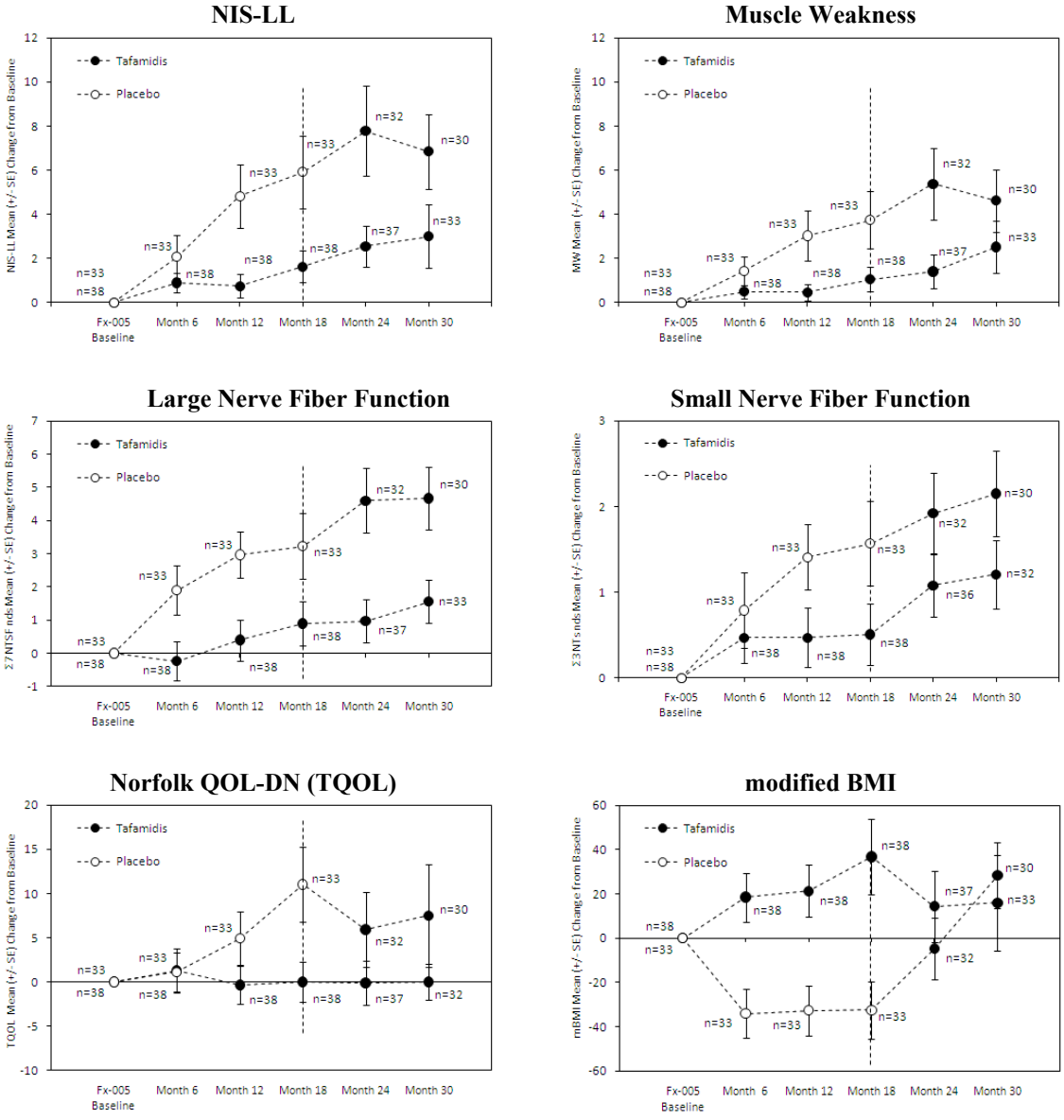
a. Results of the previous study.

b. p-Values (comparing the rate of change in the placebo-tafamidis group in Study Fx-006 to the rate of change in the previous study) based on a mixed model ANOVA. The dependent variable was the measurement at each visit. The independent variables were the study-by-treatment interaction and the time-by-study-by-treatment interaction. The intercept and time variables were modeled as random effects. The test of treatment effect was based on the time-by-study-by-treatment interaction.

c. Efficacy evaluable subjects treated with tafamidis in the previous study.

Change in Disease Progression From the Previous Study Baseline: Although the previous study and Fx-006 had separate protocols, together the studies were similar to a "delayed start" trial design. As such, the effect of tafamidis on disease progression over 30 months of follow-up could be evaluated by examining the respective changes from the previous study Baseline in the tafamidis-tafamidis and placebo-tafamidis groups. The results for the NIS-LL (including the muscle weakness subscale), TQOL, large and small nerve fiber function, and mBMI at Month 6, 12, 18, 24, and 30 months are shown in Figure 2.

Figure 2. Sustainability and Superiority of the Treatment Effect – Mean Changes in all Efficacy Endpoints From the Previous Study Baseline to Months 6, 12, 18, 24, and 30 – ITT Population (Study Fx-006)



Note: dashed vertical lines indicate initiation of open-label tafamidis administration in Study Fx-006.
ITT = intent-to-treat; BMI = modified body mass index; NIS-LL = Neuropathy Impairment Score – Lower Limb; QOL-DN = Quality of Life – Diabetic Neuropathy; TQOL = total quality of life score.

Neuropathy Impairment Score – Lower Limb Response to Treatment: In addition to the comparisons of the rate of NIS-LL change, a categorical analysis of the response to treatment (as in the previous study) was performed in which subjects with a change of <2 units in the NIS-LL were predefined to have no disease progression. These data were also supportive of the sustainability and superiority of the tafamidis treatment effect. Table 7 presents the

proportion of tafamidis-tafamidis subjects without disease progression relative to the previous study Baseline and the previous study Month 6 Visit.

Table 7. Proportion of Tafamidis Subjects Without Disease Progression – Tafamidis-Tafamidis Subjects – ITT Population (Study Fx-006)

	% (Number of Subjects Without Disease Progression/Number of Subjects)	
	<2-Point NIS-LL Change from Baseline[a]	<2-Point NIS-LL Change from Month 6[a]
Month 6[a]	68.4% (26/38)	-
Month 12[a]	71.1% (27/38)	86.8% (33/38)
Month 18[a]	63.2% (24/38)	78.9% (30/38)
Fx-006 Month 6 (month 24)	62.2% (23/37)	70.3% (26/37)
Fx-006 Month 12 (month 30)	54.5% (18/33)	69.7% (23/33)

ITT = intent-to-treat; NIS-LL = Neuropathy Impairment Score – Lower Limb.
a. Results from the previous study.

Table 8 presents the proportion of placebo-tafamidis subjects without disease progression.

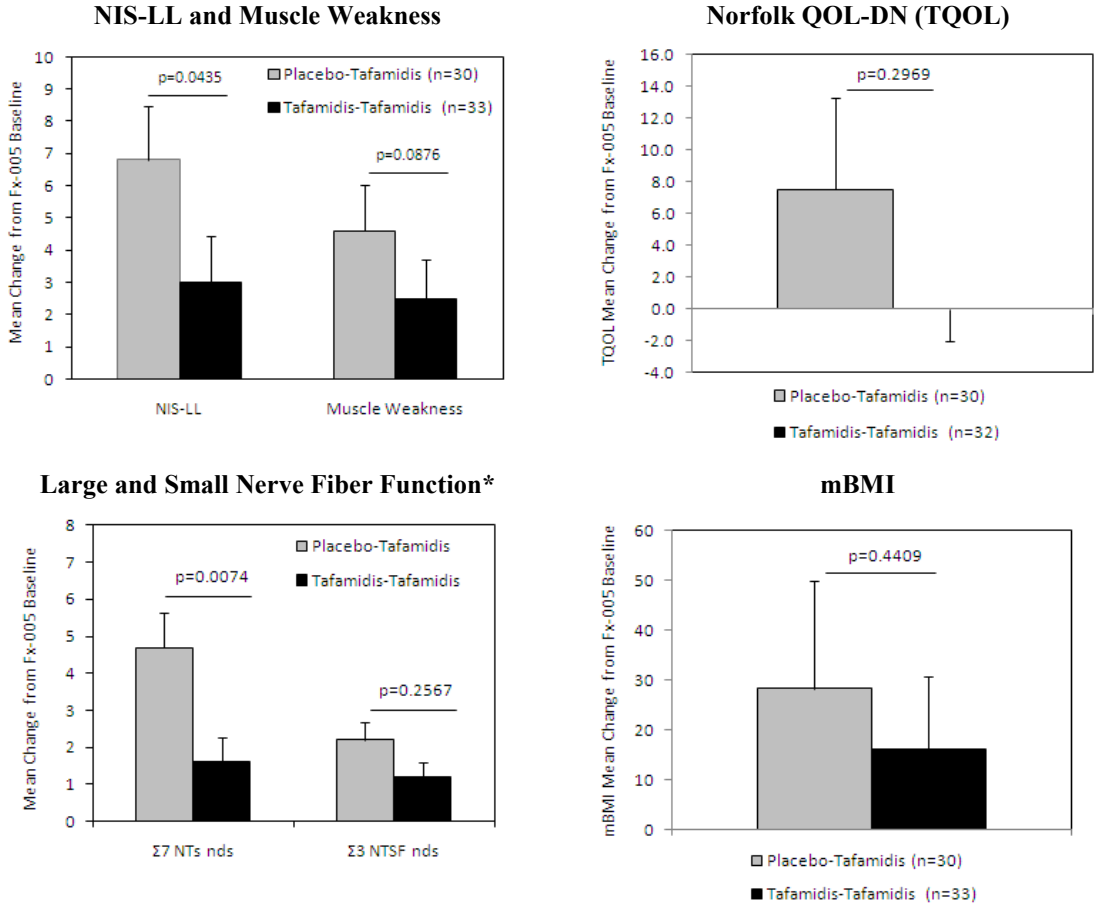
Table 8. Proportion of Subjects Without Disease Progression in the Placebo-Tafamidis Group – ITT Population (Study Fx-006)

	% (Number of Subjects Without Disease Progression/Number of Subjects)	
	Change From Baseline[a] Placebo Treatment	Change From Fx-006 Baseline Tafamidis Treatment
Month 6[a]	57.6% (19/33)	-
Month 12[a]	39.4% (13/33)	-
Month 18[a]	36.4% (12/33)	-
Fx-006 month 6 (month 24)	-	68.8% (22/32)
Fx-006 month 12 (month 30)	-	60.0% (18/30)

ITT = intent-to-treat.
a. Results from the previous study.

Early-Start Treatment Effect: To assess whether earlier initiation of tafamidis treatment results in preservation of neurologic function, the change from the previous study Baseline to the end of 30 months was compared between the treatment sequence groups. The following endpoints are presented for the ITT population: NIS-LL, Norfolk QOL-DN (TQOL), large (Σ7 NTs nds) and small (Σ3 NTSF nds) nerve fiber function, and mBMI. The results are presented in Figure 3.

Figure 3. Early-Start Treatment Effect: Mean Changes in all Efficacy Endpoints From Previous Study Baseline to Fx-006 Month 12 – ITT Population (Study Fx-006)



p-Values are based on Wilcoxon's rank sum test.
*Large nerve fiber function: n=30 in the placebo-tafamidis group; n=33 in the tafamidis-tafamidis group.
Small nerve fiber function: n=30 in the placebo-tafamidis group; n=32 in the tafamidis-tafamidis group.
NIS-LL = Neuropathy Impairment Score – Lower Limb; mBMI = modified body mass index;
QOL-DN = Quality of Life – Diabetic Neuropathy; TQOL = total quality of life score.

Intraepidermal Nerve Fiber (IENF) Density: Skin biopsies to determine IENF densities were performed at the distal leg and proximal thigh at the Fx-006 Baseline visit. However, as the number of assessments performed in the ITT population was small (11 subjects in the tafamidis-tafamidis group and 5 subjects in the placebo-tafamidis), the number was insufficient to compare between the treatment sequence groups.

Transthyretin Stabilization: TTR stabilization, as determined by the PD assay, was assessed using plasma samples obtained at enrollment into the previous study as Baseline for this extension study. Plasma samples also were collected at Week 6, and at Months 6 and 12 of Study Fx-006.

Subjects were classified as either being stabilized or not stabilized according to whether their percent stabilization was >32% (stabilized) or ≤32% (not stabilized). The results are summarized in Table 9.

Table 9. TTR Stabilization Status – ITT Population (Study Fx-006)

		Tafamidis-Tafamidis	Placebo-Tafamidis
Week 6	n (%)[a]	35/37 (94.6)	30/31 (96.8)
	95% CI	(0.81, 0.99)	(0.83, 0.99)
Month 6	n (%)[a]	34/36 (94.4)	31/32 (96.9)
	95% CI	(0.81, 0.99)	(0.83, 0.99)
Month 12	n (%)[a]	32/34 (94.1)	28/30 (93.3)
	95% CI	(0.80, 0.99)	(0.77, 0.99)

CI = confidence interval; ITT = intent-to-treat; No. = number; n = number of subjects with pre-specified criteria; TTR = Transthyretin.
a. No. of stabilized/ No. of observations.

Safety Results: For subjects, who underwent liver transplantation, reported AEs occurring on or after the date of liver transplant and prior to the End of Study Visit or Follow-Up telephone contact were not considered treatment-emergent and were summarized separately. Table 10 is a display of the overall incidence of AEs.

Table 10. Summary of Adverse Events – Safety Population (Study Fx-006)

Variable	Tafamidis-Tafamidis (N=44) n (%)	Placebo-Tafamidis (N=41) n (%)	All Subjects (N=85) n (%)
Subjects with at least 1 TEAE	37 (84.1)	40 (97.6)	77 (90.6)
Subjects with at least 1 treatment-related[a] TEAE	14 (31.8)	18 (43.9)	32 (37.6)
Subjects with at least 1 treatment-emergent SAE	5 (11.4)	4 (9.8)	9 (10.6)
Subjects with at least 1 treatment-emergent ATTR-PN-related AE	28 (63.6)	33 (80.5)	61 (71.8)
Number subjects who discontinued due to a TEAE	0	0	0
Number subjects who died	0	0	0
Number subjects with at least 1 AE post-liver transplant	2 (4.5)	0	2 (2.4)

AE = adverse events; ATTR-PN = transthyretin amyloidosis with polyneuropathy; N = total number of subjects; SAE = serious adverse event; TEAE = treatment emergent adverse event.
a. Treatment related included possibly, probably, or definitely related to study medication or unknown.

Treatment-emergent nonserious AEs are summarized in Table 11.

Table 11. Treatment-Emergent Non-Serious Adverse Events Reported in >5% of Subjects Across Treatment Groups - Safety Population

System Organ Class Preferred Term	Subject With Events (%)		
	Tafamidis–Tafamidis (N=44)	Placebo–Tafamidis (N=41)	All (N=85)
Subjects with at least 1 non-serious AE	24 (54.5%)	24 (58.5%)	48 (56.5%)
Eye disorder	5 (11.4%)	4 (9.8%)	9 (10.6%)
Punctate keratitis	3 (6.8%)	3 (7.3%)	6 (7.1%)
Dry eye	2 (4.5%)	3 (7.3%)	5 (5.9%)
Gastrointestinal disorders	6 (13.6%)	7 (17.1%)	13 (15.3%)
Diarrhoea	4 (9.1%)	3 (7.3%)	7 (8.2%)
Vomiting	2 (4.5%)	4 (9.8%)	6 (7.1%)
Infection and infestations	13 (29.5%)	16 (39.0%)	29 (34.1%)
Urinary tract infection	5 (11.4%)	6 (14.6%)	11 (12.9%)
Influenza	3 (6.8%)	7 (17.1%)	10 (11.8%)
Nasopharyngitis	5 (11.4%)	3 (7.3%)	8 (9.4%)
Upper respiratory tract infection	2 (4.5%)	3 (7.3%)	5 (5.9%)
Injury, poisoning and procedural complication	4 (9.1%)	4 (9.8%)	8 (9.4%)
Thermal burn	4 (9.1%)	4 (9.8%)	8 (9.4%)
Nervous system disorders	2 (4.5%)	6 (14.6%)	8 (9.4%)
Headache	2 (4.5%)	6 (14.6%)	8 (9.4%)
Psychiatric disorders	1 (2.3%)	5 (12.2%)	6 (7.1%)
Anxiety	1 (2.3%)	5 (12.2%)	6 (7.1%)

AEs = adverse events; N = total number of subjects.

Table 12 provides a summary of the most common treatment-emergent AEs (TEAEs) considered to be at least possibly related to study medication by the Investigator.

Table 12. Treatment-Emergent Adverse Events - Safety Population (Treatment-Related)

System Organ Class Preferred Term	Tafamidis–Tafamidis (N=44)	Placebo–Tafamidis (N=41)	All (N=85)
Subjects with at least 1 event	14 (31.8%)	18 (43.9%)	32 (37.6%)
Blood and lymphatic system disorders	0 (0.0%)	1 (2.4%)	1 (1.2%)
Anaemia	0 (0.0%)	1 (2.4%)	1 (1.2%)
Cardiac disorders	3 (6.8%)	3 (7.3%)	6 (7.1%)
Atrioventricular block second degree	2 (4.5%)	0 (0.0%)	2 (2.4%)
Bundle branch block left	0 (0.0%)	2 (4.9%)	2 (2.4%)
Atrioventricular block first degree	1 (2.3%)	0 (0.0%)	1 (1.2%)
Supraventricular extrasystoles	0 (0.0%)	1 (2.4%)	1 (1.2%)
Tachycardia	1 (2.3%)	0 (0.0%)	1 (1.2%)
Ear and labyrinth disorders	0 (0.0%)	1 (2.4%)	1 (1.2%)
Hypoacusis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Eye disorders	0 (0.0%)	3 (7.3%)	3 (3.5%)
Chorioretinopathy	0 (0.0%)	1 (2.4%)	1 (1.2%)
Dry eye	0 (0.0%)	1 (2.4%)	1 (1.2%)
Episcleritis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Ocular hypertension	0 (0.0%)	1 (2.4%)	1 (1.2%)
Gastrointestinal disorders	2 (4.5%)	5 (12.2%)	7 (8.2%)
Diarrhoea	1 (2.3%)	1 (2.4%)	2 (2.4%)
Vomiting	1 (2.3%)	1 (2.4%)	2 (2.4%)
Abdominal pain	0 (0.0%)	1 (2.4%)	1 (1.2%)
Abdominal pain upper	0 (0.0%)	1 (2.4%)	1 (1.2%)
Dyspepsia	0 (0.0%)	1 (2.4%)	1 (1.2%)
Flatulence	0 (0.0%)	1 (2.4%)	1 (1.2%)
Gastritis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Nausea	0 (0.0%)	1 (2.4%)	1 (1.2%)
General disorders and administration site conditions	0 (0.0%)	1 (2.4%)	1 (1.2%)
Feeling hot	0 (0.0%)	1 (2.4%)	1 (1.2%)
Infections and infestations	1 (2.3%)	6 (14.6%)	7 (8.2%)
Urinary tract infection	1 (2.3%)	1 (2.4%)	2 (2.4%)
Influenza	0 (0.0%)	1 (2.4%)	1 (1.2%)
Meningitis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Pharyngitis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Rhinitis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Sinusitis	0 (0.0%)	1 (2.4%)	1 (1.2%)
Tooth infection	0 (0.0%)	1 (2.4%)	1 (1.2%)
Vaginal infection	0 (0.0%)	1 (2.4%)	1 (1.2%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (2.4%)	1 (1.2%)
Foot fracture	0 (0.0%)	1 (2.4%)	1 (1.2%)
Investigations	1 (2.3%)	1 (2.4%)	2 (2.4%)
Electrocardiogram T wave biphasic	0 (0.0%)	1 (2.4%)	1 (1.2%)
Hepatic enzyme increased	1 (2.3%)	0 (0.0%)	1 (1.2%)
Musculoskeletal and connective tissue disorders	1 (2.3%)	3 (7.3%)	4 (4.7%)
Muscle fatigue	0 (0.0%)	2 (4.9%)	2 (2.4%)
Arthralgia	0 (0.0%)	1 (2.4%)	1 (1.2%)
pain in extremity	1 (2.3%)	0 (0.0%)	1 (1.2%)
Neoplasms benign, malignant and	1 (2.3%)	0 (0.0%)	1 (1.2%)

Table 12. Treatment-Emergent Adverse Events - Safety Population (Treatment-Related)

System Organ Class Preferred Term	Tafamidis–Tafamidis (N=44)	Placebo–Tafamidis (N=41)	All (N=85)
unspecified (including cysts and polyps)			
Lymphoma	1 (2.3%)	0 (0.0%)	1 (1.2%)
Nervous system disorders	3 (6.8%)	5 (12.2%)	8 (9.4%)
Headache	1 (2.3%)	3 (7.3%)	4 (4.7%)
Dysaesthesia	1 (2.3%)	0 (0.0%)	1 (1.2%)
Hypoaesthesia	1 (2.3%)	0 (0.0%)	1 (1.2%)
Neuralgia	0 (0.0%)	1 (2.4%)	1 (1.2%)
Paraesthesia	0 (0.0%)	1 (2.4%)	1 (1.2%)
Restless legs syndrome	0 (0.0%)	1 (2.4%)	1 (1.2%)
Renal and urinary disorders	1 (2.3%)	0 (0.0%)	1 (1.2%)
Haematuria	1 (2.3%)	0 (0.0%)	1 (1.2%)
Respiratory, thoracic and mediastinal disorders	1 (2.3%)	0 (0.0%)	1 (1.2%)
Pharyngolaryngeal pain	1 (2.3%)	0 (0.0%)	1 (1.2%)
Skin and subcutaneous tissue disorders	3 (6.8%)	0 (0.0%)	3 (3.5%)
Alopecia	1 (2.3%)	0 (0.0%)	1 (1.2%)
Eczema	1 (2.3%)	0 (0.0%)	1 (1.2%)
Skin lesion	1 (2.3%)	0 (0.0%)	1 (1.2%)

All AEs were coded using MedDRA dictionary Version 10.0. A subject with multiple events per system organ class or preferred term is counted only once per system organ class when counting subjects. Related relationship includes Possible, Probable, Definite or Missing relationship.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Table 13 is a by-subject summary of the SAEs reported in this study, presented by treatment group. A total of 23 treatment-emergent SAEs were reported by 9 subjects (5 from the tafamidis-tafamidis group and 4 from the tafamidis-placebo group). Four subjects had SAEs related to infection (1 from the tafamidis-tafamidis group and 3 from the placebo-tafamidis group). Of note, re-challenge with tafamidis in all subjects was negative. The next most frequent SAEs were gastrointestinal disorders (nausea and vomiting). Both infection and gastrointestinal disorders are frequently reported events in ATTR-PN patients. A review of SAEs did not indicate any apparent causal relationship to tafamidis. There were no apparent safety issues identified in the post-transplant setting.

Table 13. By-Subject Listing of Treatment-Emergent Serious Adverse Events - Safety Population (Study Fx-006)

Treatment Group Serial Number	Preferred Term	Relationship	Outcome
Tafamidis-Tafamidis			
1	Hypersensitivity	Unrelated	Recovered
2	Skin lesion	Unrelated	Recovered
	Vomiting	Unrelated	Recovered
3	Lymphoma	Possible	Ongoing
4	Nausea	Unrelated	Recovered
	Vomiting	Unrelated	Recovered
5	Catheter sepsis	Unrelated	Recovered
	Catheter site infection	Unrelated	Recovered.
	Blood electrolytes decreased	Unrelated	Recovered
Placebo-Tafamidis			
1	Urinary tract infection	Unrelated	Recovered
	Dehydration	Unrelated	Recovered
2	Meningitis	Possible	Recovered
3	Anaemia	Unrelated	Recovered
	Infection	Unrelated	Recovered
	Osteomyelitis	Unrelated	Recovered with sequelae
4	Nausea	Unrelated	Recovered
	Nausea	Unrelated	Recovered
	Vomiting	Unrelated	Recovered
	Vomiting	Unrelated	Recovered
	Vomiting	Unrelated	Recovered
	Vomiting	Unrelated	Recovered
	Vomiting	Unrelated	Recovered
	Vomiting	Unrelated	Recovered

No patient died or discontinued due to an AE.

Other Safety Results: The mean changes from Fx-006 Baseline for clinical laboratory parameters were performed for hematology, serum chemistry, and urinalysis parameters. While there were a few mean changes over time in laboratory values, most were transient and were not considered clinically relevant between the treatment sequence groups.

TTR and retinol binding protein (RBP) values in the tafamidis-tafamidis group were constant over time. In the placebo-tafamidis group, TTR values increased from Baseline beginning at the first assessment timepoint (mean Week 6 increase of 7.5 mg/dL) and remained constant at approximately 29 mg/dL. Similar trends of a smaller magnitude were observed for RBP in the placebo-tafamidis group. These results were similar to the observations in the previous study tafamidis arm in which the initial increase in TTR (6.4 mg/dL at Week 4) and RBP (range 2.0 to 11.0 mg/dL) was maintained at subsequent time points, whereas in the placebo arm TTR levels decreased with no change in RBP.

Average changes over time in vital sign parameters were minor and not clinically relevant; no trends were observed and outcomes were similar between treatment sequence groups. There was no systematic effect of tafamidis on blood pressure, pulse, or on the incidence of orthostasis.

Overall the most commonly reported physical examination abnormality was in the "other" category for body system, reported by 9 of 85 subjects overall (10.6%). The investigator-reported abnormalities included the following: infected thermal burn on left foot, painful palpitation of the hypogastrium, swollen foot with skin bruises from trauma, burn with ulcer at left heel and lower third of left leg, pharynx ruborization, cutaneous erythematous lesions with pruritis in both feet and left leg, enlarged lymph nodes in the right groin and right side of neck (in a subject undergoing treatment for lymphoma), decreased sensitivity in heel and ankle, right leg fracture, gait impairment and muscular leg atrophy, and progression of muscular weakness in extremities.

Average ECHO values were normal in this subject population, and similar between treatment sequence groups at Baseline, with no clinically relevant changes at Months 6 and 12.

There was no cardiac risk associated with tafamidis administration as evidenced by multimodality assessments (i.e., ECHO, ECG, Holter monitoring, and cardiac biomarkers). Treatment with tafamidis did not result in clinically relevant abnormal physical examination findings, or abnormalities in eye/fundal examination findings.

CONCLUSION: This study demonstrated that subjects administered tafamidis for 30 months had better neurological status than subjects who received tafamidis for 12 months only. In addition, once daily dosing with 20-mg tafamidis appeared safe and well tolerated, with no safety issues associated with long-term (up to 30 months) treatment. The outcomes from this study corroborate the findings from the previous study, in which tafamidis-treated subjects had slower disease progression than their placebo-treated counterparts. Moreover, these outcomes provide longer-term safety data supportive of the tolerability of tafamidis in the ATTR-PN population. In total, these data suggest that early initiation of tafamidis therapy would result in improved clinical outcomes, including ambulation, and ultimately improved survival.