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GENERIC DRUG NAME and/or COMPOUND NUMBER: Tafamidis / Fx-1006A

PROTOCOL NO.: FX-005 (B3461020)

PROTOCOL TITLE: Safety and Efficacy of Orally Administered Fx-1006A in Patients With Familial Amyloid Polyneuropathy (FAP): A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Study

Study Centers: A total of 8 centers enrolled subjects; 2 centers in Portugal, and 1 center each in Argentina, Brazil, France, Germany, Spain, and Sweden.

Study Initiation Date and Final Completion Date: 16 January 2007 and 26 May 2009

Phase of Development: Phase 2/3

Study Objectives:

Primary Objectives:

- To evaluate the effect of FX-1006A on disease progression in subjects with FAP.
- To evaluate the safety and tolerability of 18 months of treatment with Fx-1006A in subjects with FAP.

Secondary Objectives:

- To determine the pharmacodynamic stabilization effect of Fx-1006A on human V30M (valine replaced by methionine at position 30) TTR (transthyretin).
- To characterize the population pharmacokinetics in subjects with FAP.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, multicenter, international study designed to evaluate the safety and efficacy of tafamidis compared to placebo during 18 months of treatment in subjects diagnosed with transthyretin familial amyloid polyneuropathy (TTR-FAP), and with a confirmed V30M mutation and positive amyloid biopsy. One hundred twenty subjects (60 subjects per group) were to be enrolled during the study. The study was conducted on an outpatient basis, with maximum duration of subject participation being approximately 20 months, including the screening period (Days -30 to -1), the treatment period (18 months), and a final telephone contact (1 month after the last dose of study medication).

Subjects who provided written informed consent were evaluated for eligibility during the screening period. Screening laboratory evaluations were completed within 3 days before Baseline (Day 0) in order for results to be available and reviewed before enrollment. Neuropathy impairment score – lower limb (NIS-LL) testing was performed twice within a 1 week period before dosing; the 2 tests were performed at least 24 hours apart but within a 1 week period, preferably at the same time of day. Both tests were completed before study medication was taken on Day 1.

Eligible subjects (based on screening assessments) were enrolled and randomly assigned (in a 1:1 ratio) to 1 of the 2 treatment groups at Baseline (Day 0). After completion of screening and baseline assessments and enrollment in the study, subjects began taking study medication at home on Day 1. Subjects were considered to have completed the study after the Month 18 Visit (End of Study Visit [EOS]). Subjects were contacted by telephone 1 month following the EOS Visit (Month 19) for determination of ongoing and post study adverse events (AEs).

Schedule of events is presented in Table 1.

Table 1. Schedule of Events

Evaluation	Screening		Baseline Visit	← Outpatient Follow-Up →								
	Screen 1 (Days -30 to -1)	Screen 2 (Days -7 to 0)	Day 0 Visit	Day 1	2 Wk Visit ±2 Days	4 Wk Visit ±2 Days	8 Wk Visit ±1 Wk	12 Wk Visit ±1 Wk	6 Mo Visit ±2 Wks	9 Mo Visit ±2 Wks	12 Mo Visit ±2 Wks	18 Mo Visit ±2 Wks
Informed consent	X											
Medical history / demographics	X											
Review of entrance criteria	X		X									
Biopsy to confirm amyloid[a]	X[a]											
Physical examination	X								X		X	X
Abbreviated PE					X	X	X	X				
Body weight	X								X		X	X
Body height	X											
12-Lead ECG	X		X			X			X		X	X
Vital signs	X		X		X	X	X	X	X	X	X	X
Serology[b]	X[b]											
Urine pregnancy test (females of child-bearing potential only)	X		X		X	X	X	X	X	X	X	X
Hematology, coagulation panel, serum chemistry, urinalysis	X		X		X	X	X	X	X	X	X	X
Laboratory tests for subjects with negative or no biopsy only (HbA1c and Vitamin B12)[c]	X											
Randomization/enrollment			X									
QST for vibration perception in the feet utilizing CASE 4	X											
NIS-LL[d]		X[e]	X[e]						X[d]		X[d]	X[d]
QST/HRDB/NCS			X						X		X	X
Norfolk QOL-DN			X						X		X	X
Echocardiography[f]			X						X		X	X
Eye exam/fundal photography[f]			X						X		X	X
Study medication compliance					X	X	X	X	X	X	X	X
Study medication administration			X			X	X	X	X	X	X[g]	
First study medication dose				X								
Mouth swab for confirmation of V30M genotype			X									
Blood sample for PK analysis			X				X		X		X[h]	X[h]

Table 1. Schedule of Events

Evaluation	Screening		Baseline Visit	← Outpatient Follow-Up →								
	Screen 1 (Days -30 to -1)	Screen 2 (Days -7 to 0)	Day 0 Visit	Day 1	2 Wk Visit ±2 Days	4 Wk Visit ±2 Days	8 Wk Visit ±1 Wk	12 Wk Visit ±1 Wk	6 Mo Visit ±2 Wks	9 Mo Visit ±2 Wks	12 Mo Visit ±2 Wks	18 Mo Visit ±2 Wks
Blood sample for TTR stabilization assay			X				X		X		X	X
Adverse events[i]	Monitored on a continuous basis from date ICF obtained through the Month 19 telephone contact											
Concomitant medications[i]												

ECG = Electrocardiogram; HBsAg = antigen of the hepatitis B virus HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; HRDB = Heart rate response to deep breathing; Mo = month; NCS = Nerve conduction studies; NIS-LL = Neuropathy Impairment Score – Lower Limb; QOL-DN = Quality of life – diabetic neuropathy; QST = Quantitative sensory testing; PK = Pharmacokinetics; TTR = Transthyretin; V30M = Valine replaced by methionine at position 30; Wk = Week.

a. Biopsy must had been performed within 5 years of enrollment. If >5 years, biopsy must be repeated at the investigative site.
b. All subjects were tested for HbsAg, anti-HCV, and HIV during the screening period only.
c. These activities were included in the final protocol under Portugal-specific Amendment 6 and Germany-specific Amendment 3 and were never implemented. Subjects with negative biopsies were not enrolled under these amendments and these activities were, therefore, not performed.
d. 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 study.
e. NIS-LL testing was performed 2 times at least 24 hours apart within a 1-week period before and/or at the Baseline visit. Both evaluations were completed prior to study medication administration.
f. Baseline echocardiography and eye examination/fundal photography could had been performed during the screening period only in cases where scheduling with cardiology and/or the ophthalmologist did not permit the examinations at Baseline.
g. Study medication administration at 15 months was via courier as no clinic visit was scheduled.
h. Two blood samples for measurement tafamidis levels were collected from each subject at Months 12 and 18, with the first sample collected as soon as the subject arrived at the clinical site (but after Norfolk QOL-DN testing); the second sample was collected immediately before the subject left the site, after all other scheduled procedures were completed
i. Monthly telephone contact (±1 week of the scheduled date) to monitor adverse events and concomitant medications including a final telephone contact 1 month after the end-of-study visit for final safety assessment (Month 19).

Number of Subjects (Planned and Analyzed): A total of 120 subjects were planned to be enrolled in this study. A total of 128 subjects were enrolled in this study (10 in the Argentina, 13 in the Brazil, 9 in France, 6 in Germany, 78 in Portugal, 2 in Spain and 10 in Sweden).

Diagnosis and Main Criteria for Inclusion: Male and female subjects between the ages of 18 and 75 years, inclusive, diagnosed with TTR-FAP with documented V30M TTR mutation and positive biopsy were enrolled. All subjects were to provide written informed consent to participate and be, in the Investigator's opinion, willing and able to comply with the study medication regimen and all other study requirements.

Study Treatment: Tafamidis meglumine and matching placebo were supplied as opaque 12, oblong, soft gelatin capsules. Tafamidis meglumine capsules were filled with a suspension containing 20 mg of tafamidis to be taken orally.

Subjects were provided blinded study medication and were instructed to self-administer their medication at home once daily for 18 months. The subjects received a 1 month supply of study medication at 4 week intervals to take home for self-administration during the first 3 months of the study. Additional supply of study medication was dispensed to subjects at pre-scheduled follow-up visits every 3 months. At Month 15, the final study medication supply (3 months) was sent to the subjects via courier.

Subjects were instructed to take study medication at the same time each day, orally with water and without regard to food intake, throughout the treatment period.

Efficacy and Safety Endpoints:

Efficacy Endpoints:

Primary Efficacy Endpoints:

- Response to treatment at Month 18, as indicated by either improvement (decrease from Baseline) or stabilization (change from Baseline of 0 to <2) in the NIS-LL score. The NIS-LL score for each study visit based on the average of 2 scores taken at least 24 hours apart within a 1-week period for each study visit.

- Change from Baseline to 18 months in the Total Quality of Life (TQOL) score, as measured by the Norfolk QOL-DN (quality of life – diabetic neuropathy).

Secondary Efficacy Endpoints:

- Response to treatment, in percentage of subjects as indicated by either improvement or stabilization in the NIS-LL score, at Months 6 and 12.

- A continuous analysis of the change from Baseline to Months 6, 12, and 18 in NIS-LL.

- Change from Baseline to 6 and 12 months in the TQOL score, as measured by the Norfolk QOL-DN.

- Change from Baseline to 6, 12 and 18 months in the 5 domains of the Norfolk QOL-DN.

- Change from Baseline through Month 18 in Summated 7-composite score and Summated-3 composite score, as measured by nerve conduction studies (NCS), and quantitative sensory testing (QST; ie, heat, pain, and cooling thresholds) utilizing CASE IV testing.

- Change from Baseline through Months 6, 12, and18 in modified Body Mass Index (mBMI).

- TTR stabilization through Month 18, as measured by a validated immunoturbidimetric assay.

Safety Endpoints:

- Incidence of subjects experiencing treatment-emergent serious AEs (SAEs).

- Incidence of subjects experiencing treatment-emergent ≥Grade 3 AEs.

- Incidence of subjects experiencing treatment-emergent ≥Grade 3 clinical laboratory findings.

- Incidence of subjects with treatment-emergent echocardiography 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 discontinuing from the study because of clinical or laboratory AEs

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

Statistical Methods:

There were 3 pre-specified analysis populations:

- Intent-to-treat (ITT): All randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline efficacy assessment for both NIS-LL and Norfolk QOL-DN or discontinued the study due to death or liver transplant.

- Efficacy evaluable: All ITT subjects with non-missing Month 18 NIS-LL and TQOL scores, who took at least 80% of study medication, and had no major protocol violations.

- Safety: All randomized subjects who received at least 1 dose of study medication.

Efficacy Analysis: Unless otherwise specified, all efficacy analyses were conducted on the ITT and efficacy evaluable populations. Superior treatment efficacy of tafamidis was established if statistically significant (2-sided; alpha of 0.05) differences favoring tafamidis were demonstrated for each of the co-primary endpoints. Both co-primary endpoints were evaluated in the ITT population using the last observation carried forward (LOCF) to impute missing data at Month 18. For the NIS-LL responder analysis, subjects who discontinued due to liver transplantation or death were categorized as non-responders. Pre-specified secondary analyses of the primary endpoints included (1) a sensitivity analysis of the NISLL in which response was imputed for subjects who underwent liver transplantation and (2) analyses in subjects with non-missing NIS-LL and TQOL scores at Month 18 and no major protocol violations (Efficacy evaluable population). A Chi-square test for proportions was used to compare NIS-LL response rates between treatment groups. For the Norfolk QOL-DN, an analysis of covariance model with baseline as covariate was used to compare treatment group TQOL scores. The response to treatment at Month 18 in the NIS-LL was modeled as a function of treatment and other prognostic covariates such as gender, age, duration of TTR-FAP -related symptoms, and baseline NIS-LL score using logistic regression methods. Secondary endpoints were analyzed using a repeated measures analysis of variance (ANOVA) model with an unstructured matrix, treatment, month, and treatment-by-month interaction as fixed effects and subject as a random effect. Within treatment group analyses were also performed for all secondary efficacy endpoints (except NIS-LL) using a 1 sample t-test to determine whether the change from Baseline was significantly different from zero. An observed case method was used in these ANOVA models.

Interim Analysis: A Data Monitoring Committee (DMC) monitored the safety and efficacy of the trial. Blinded safety summaries were provided to the DMC at 3, 6, 12, 18, and 24 months after enrollment commenced. An interim safety analysis was conducted after 25% of subjects completed the 6-month evaluation. No safety concerns were raised by the DMC and the trial continued. An interim efficacy and safety analysis was conducted after 80% of subjects completed the 12-month evaluation (or discontinued prior to that time) to determine whether the trial could be ended before the planned completion date. The committee recommended that the trial continue. The interim analysis was unblinded, but the blind remained unbroken for subjects and Investigators, and the Sponsor was not aware of the results of the interim analysis; p-values were adjusted accordingly.

RESULTS

Subject Disposition and Demography: Disposition of subjects is presented in Table 2.

Table 2. Subject Disposition and Subjects Analyzed

	Tafamidis 20 mg	Placebo	All Subjects
Subjects screened			162
Screen failures			34
Subjects randomized	65	63	128
Subjects receiving at least one study drug dose	65 (100.0%)	63 (100.0%)	128 (100.0%)
Subjects completing study	47 (72.3%)	44 (69.8%)	91 (71.1%)
Subjects who prematurely withdrew	18 (27.7%)	19 (30.2%)	37 (28.9%)
Reasons for withdrawal			
Adverse event	4 (6.2%)	3 (4.8%)	7 (5.5%)
Liver transplant	13 (20.0%)	13 (20.6%)	26 (20.3%)
Other	0 (0.0%)	1 (1.6%)	1 (0.8%)
Subject withdrew consent	1 (1.5%)	2 (3.2%)	3 (2.3%)
Safety population	65 (100.0%)	63 (100.0%)	128 (100.0%)
ITT population	64 (98.5%)	61 (96.8%)	125 (97.7%)
Efficacy evaluable population	45 (69.2%)	42 (66.7%)	87 (68.0%)

ITT = intent-to-treat.
All other percentages were based on the number of subjects who received at least 1 dose of study drug.

A summary of demographics and baseline disease characteristics for the ITT population is presented in Table 3. The treatment groups were similar with respect to demographic characteristics. The mean age of all subjects was approximately 39 years, with approximately 54% of subjects female and approximately 88% of subjects Caucasian.

Baseline characteristics were examined for the subgroup of subjects (N = 13 in each treatment group) who underwent liver transplantation. While there were no statistically significant differences between the treatment groups for any baseline characteristic in this subgroup, median symptom duration in transplant subjects was longer (medians of 57.9 and 34.5 months in the tafamidis and placebo groups, respectively) than non-transplant subjects (medians of 22.3 and 21.4 months, respectively). Consistent with this observation, transplant subjects had higher baseline NIS-LL scores (median of 10.0) than non-transplant subjects (medians of 4.0). Thus, undergoing liver transplant tended to be associated with duration of disease and not with treatment assignment in this study.

Table 3. Demographics and Baseline Disease (ITT Population)

	Tafamidis 20 mg N=64	Placebo N=61	p-Value[a]
Age, years			
Mean (SD)	39.8 (12.7)	38.4 (12.9)	
Median	35.5	34.0	
Range	25, 74	22, 71	0.339
Age group, n (%)			
≤65 years	59 (92.2)	58 (95.1)	
>65 years	5 (7.8)	3 (4.9)	0.510
Gender, n (%)			
Male	32 (50.0)	26 (42.6)	
Female	32 (50.0)	35 (57.4)	0.410
Race, n (%)			
Caucasian	56 (87.5)	54 (88.5)	
Latin American	6 (9.4)	6 (9.8)	
Not available	2 (3.1)	1 (1.6)	0.736
mBMI at screening			
Mean (SD)	1004.59 (165.2)	1011.54 (212.9)	
Median	974.7	983.8	
Range	655.1, 1510.4	533.3, 1581.5	0.739
Height, cm			
Mean (SD)	166.8 (10.1)	166.6 (11.2)	
Median	167.0	165.5	
Range	147, 186	149, 191	0.843
Weight, kg			
Mean (SD)	64.1 (11.9)	63.9 (13.4)	
Median	62.0	64.0	
Range	39, 91	32, 100	0.962
Baseline NIS-LL (scale 0 to 88)			
Mean (SD)	8.4 (11.4)	11.4 (13.5)	
Median	4.0	6.0	
Range	0, 54	0, 57	0.089
Baseline TQOL (scale -2 to 138)			
Mean (SD)	27.3 (24.2)	30.8 (26.7)	
Median	19.0	22.0	
Range	-1, 110	0, 107	0.401
Duration of symptoms, months			
Mean (SD)	47.0 (48.4)	34.7 (32.9)	
Median	28.0	21.0	
Range	3, 268	2, 133	0.319

ITT = intent-to-treat; mBMI = modified body mass index; n = number of subjects with observation; N = evaluable number of subject; NIS-LL = neuropathy impairment score-lower limb; SD = standard deviation; TQOL = total quality of life.

a. p-values based on Wilcoxon's rank sum test for continuous variables and Cochran-Mantel-Haenszel test for categorical variables.

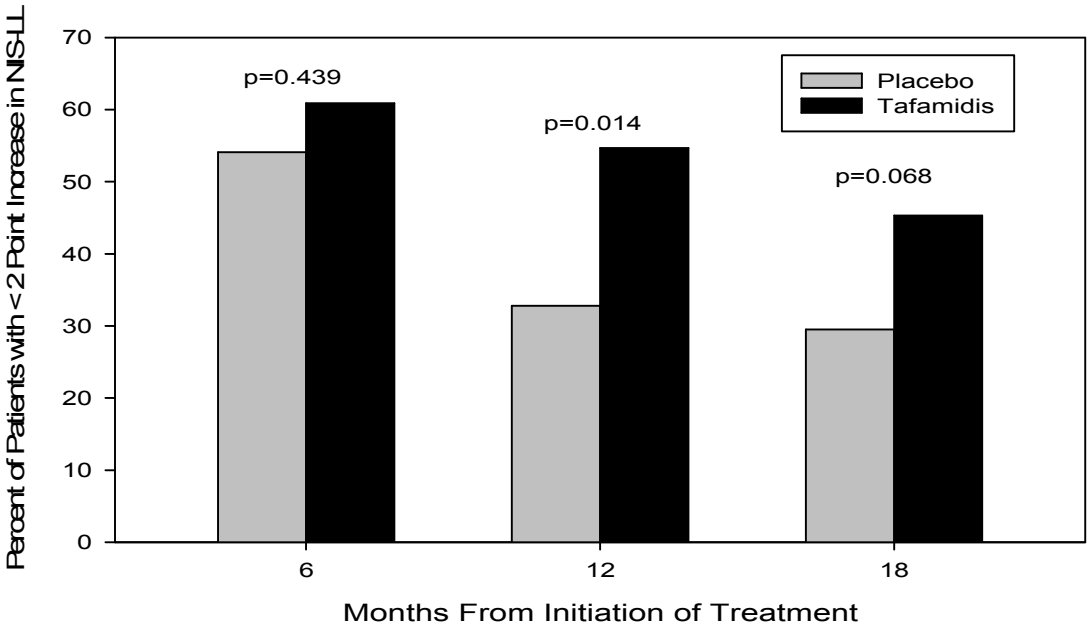
Efficacy Results:

Primary Endpoints: There were 2 co-primary endpoints in this study: the NIS-LL and the TQOL. The analysis of the NIS-LL is presented first (including the primary analysis of this variable at the Month 18 time point, the changes from Baseline to each on-treatment time point, the rate of disease progression, sensitivity analysis, and the subscale assessments), followed by the analysis of the TQOL (including the primary analysis of this variable at the Month 18 time point, the change from Baseline to each on-treatment time point, the rate of disease progression, the within-group changes from Baseline, and subscale [domain] assessments).

NIS-LL Categorical Analysis: Figure 1 provides the percent of subjects responding at each study visit (including the primary efficacy assessment of the NIS-LL at Month 18).

Outcomes for the NIS-LL at Month 18 demonstrated that 45.3% subjects in the tafamidis group had an increase in the NIS-LL of <2 at Month 18, compared with 29.5% subjects in the placebo group (p=0.068). The analysis of NIS-LL response over time demonstrates that more subjects treated with tafamidis experienced slowing of disease progression between 6 and 12 months of treatment, and was statistically significant (compared with placebo) by Month 12.

Figure 1. NIS-LL Response[a, b] to Treatment by Study Visit – Co-Primary Endpoint at Month 18 (ITT Population, LOCF)



ITT = intent-to-treat; LOCF = last observation carried forward;
NIS-LL = neuropathy impairment score - lower limb.

[a] LOCF was used to impute missing values at Months 12 and 18; subjects who discontinued due to liver transplantation or death were categorized as non-responders.

[b] p-value based on Chi-square test for proportions.

It was expected that most subjects enrolling in the trial would be on the liver transplantation waiting list and that some of these subjects would undergo liver transplantation when an organ match became available. A pre-specified sensitivity analysis was performed on the effect of liver transplantation on the NIS-LL categorical responder analysis. The results are shown in Table 4. These outcomes demonstrate outcomes similar to those of the primary analysis, and, importantly, that the tafamidis group had a statistically significantly higher percent of subjects with no disease progression than observed in the placebo group. This analysis supports the robustness of the study findings.

Table 4. NIS-LL Sensitivity Analysis[a] with Imputed Responses for Liver Transplant Subjects (ITT Population)

		Tafamidis 20 mg N=64	Placebo N=61	Tafamidis vs Placebo
NIS-LL responders	n (%) responders	35 (54.7)	22 (36.1)	
	95% confidence interval	42.5%, 66.9%	24.0%, 48.1%	
	p-value[b]			0.0367

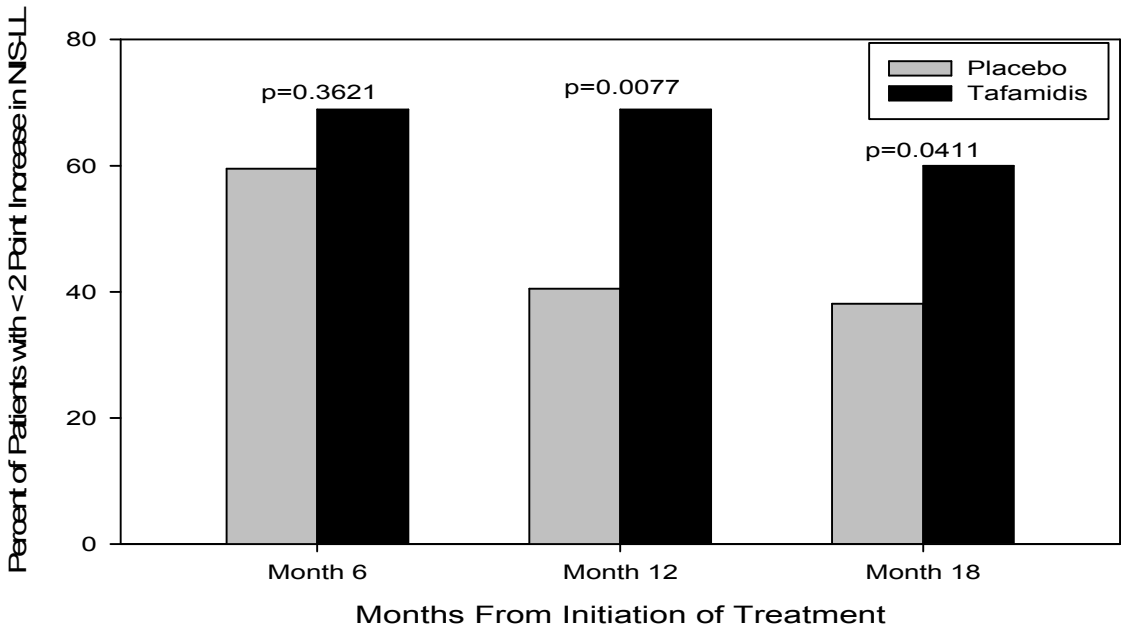
ITT = intent-to-treat; n = number of subjects with observation; N = evaluable number of subject; NIS-LL = neuropathy impairment score - lower limb.

a. A logistic regression model was fitted with NIS-LL response at Month 18 as dependent variable, treatment and baseline NIS-LL as independent variables. For each treatment group, the predicted probability of NIS-LL response was a function of baseline NIS-LL score. Using the median baseline NIS-LL score for subjects who underwent liver transplantation, it was possible to obtain an estimated probability of NIS-LL response for these subjects. This probability was used to impute NIS-LL response for subjects who underwent liver transplantation.

b. Based on Chi-square test for proportions.

Figure 2 provides a presentation of the analysis of the NIS-LL response to treatment using the efficacy evaluable population at each of the 3 on-treatment time points (including the primary time point at Month 18). Outcomes for the efficacy evaluable population assessment of the NIS-LL response at Month 18 demonstrated that 60.0% of subjects in the tafamidis group had no disease progression at Month 18, compared with 38.1% subjects in the placebo group (p=0.041).

Figure 2. NIS-LL Response[a,b] to Treatment by Study Visit – Co-Primary Endpoint at Month 18 (Efficacy Population)

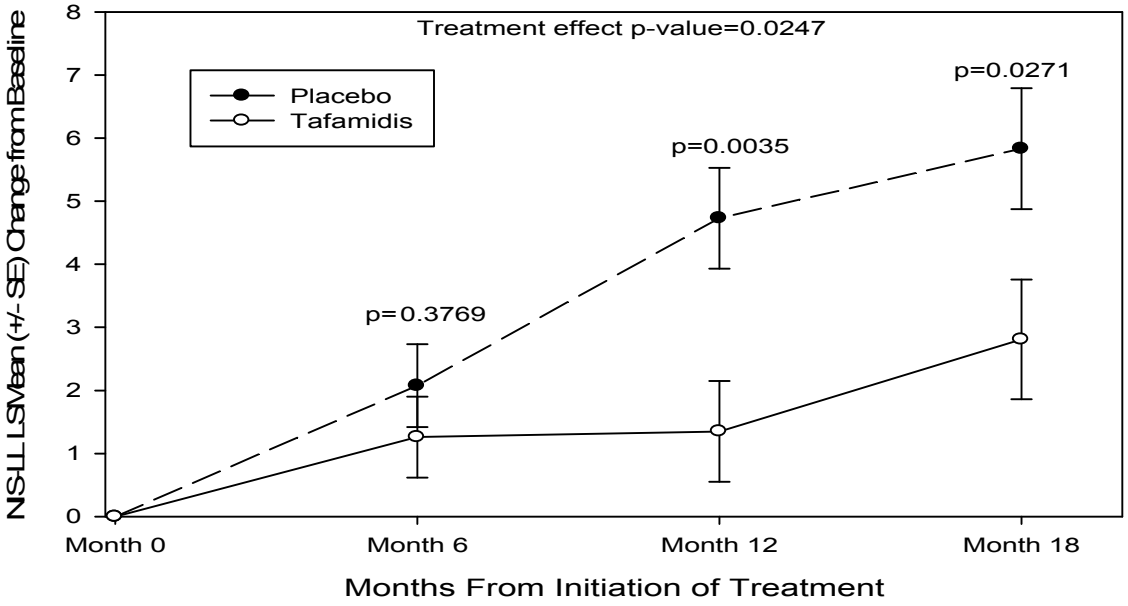


[a] Observed cases were used.
[b] p-value based on Chi-square test for proportions.
NIS-LL = neuropathy impairment score - lower limb.

NIS-LL Continuous Change Analysis: In addition to the categorical analysis of the NIS-LL described above, a continuous change from Baseline analysis was performed. Figure 3 provides a descriptive presentation (least square [LS] Means + standard error [SE]) of the NIS-LL change scores over time for each treatment group, (including assessment at the Month 18 primary time point). This analysis provides the most thorough picture of the time-course of the treatment effect, allowing for identification of the earliest protocol-scheduled time point at which an effect becomes evident, the time point at which the effect becomes statistically significant, and whether there is persistence of the effect over the course of the 18-month treatment period. p-values (including the overall treatment effect) were from the pre-specified repeated measures model.

During the 18-month treatment period, the tafamidis group demonstrated significantly less average worsening of impairment (as measured by LSMean changes in the NIS-LL) than did the placebo group (overall treatment effect p=0.0247), with the differences significant and clinically meaningful by Month 12. By Month 18, the LSMean (SE) difference in NIS-LL between the placebo group and the tafamidis group was 3.024 (1.351), reflecting both a statistical (p-value = 0.0271) and clinically meaningful difference (≥2). This analysis clearly demonstrates that subjects treated with tafamidis experienced early benefit from treatment that increased over time and was maintained through the completion of the 18-month treatment period.

Figure 3. NIS-LL LSMean (SE) Change From Baseline to On-Treatment Visits (ITT Population, Observed Cases)



p-values for overall treatment effect and by-visit treatment effects were based on a repeated measures ANOVA with change from Baseline as the dependent variable, an unstructured covariance matrix, treatment, month and treatment x month as fixed effects and subject as a random effect in the model.
ANOVA = analysis of variance; ITT = intent-to-treat; LS = least square; NIS-LL = neuropathy impairment score - lower limb; SE = standard error.

The rate of disease progression, measured as the rate of change from Baseline in NIS-LL per month, is summarized by treatment group in Table 5. The rate of change analysis demonstrates that the tafamidis group demonstrated an average increase of 0.165 NIS-LL units per month, while the placebo group demonstrated an average increase of 0.345 NIS-LL units per month, reflecting a statistically significant difference (p-value = 0.018) in the rate of progression of disease as measured by NIS-LL.

Table 5. NIS-LL Rate of Change per Month (ITT Population)

NIS-LL	Tafamidis 20 mg	Placebo	Rate Difference (Tafamidis - Placebo)
Units/month (SE) 95% confidence interval p-value	0.165 (0.0533)	0.345 (0.0538)	-0.181 (0.0757) -0.330, -0.031 0.0179

ITT = intent-to-treat; NIS-LL = neuropathy impairment score - lower limb; SE = standard error.

The NIS-LL was comprised of 3 subscales: muscle weakness, reflexes, and sensation. In order to better understand which (if any) subscale contributed the greatest effect towards the overall NIS-LL changes from Baseline, an analysis of the NIS-LL subscales was performed. The baseline (pre-treatment) comparison between the treatment groups for each of these subscales is provided in Table 6. While the placebo group tended to had numerically higher

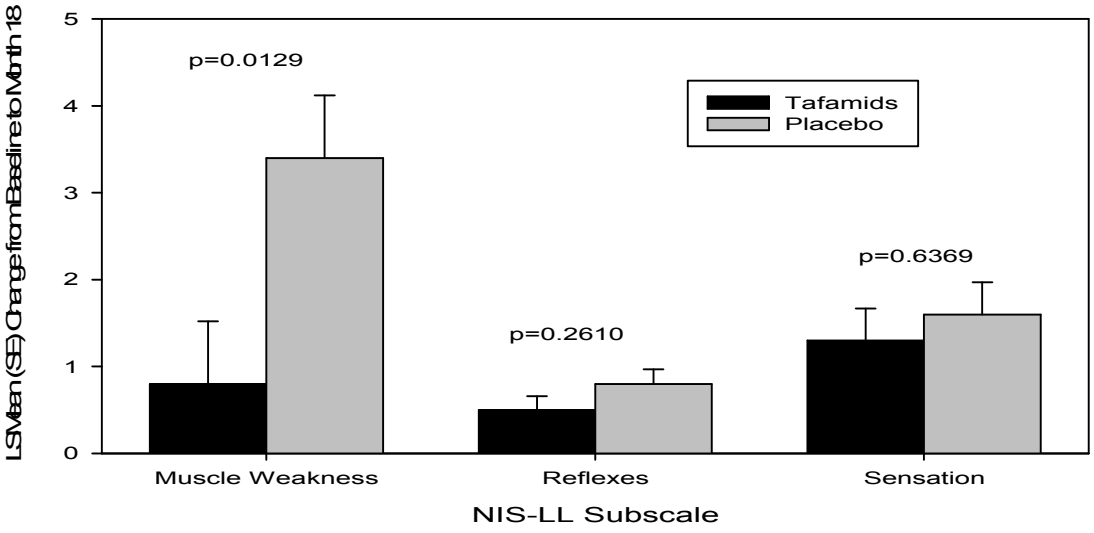
(worse) scores for each subscale than the tafamidis group (with the largest difference being for the sensation subscale), the treatment-group differences were not statistically significant for any of the subscales. The analysis of the treatment effect at the Month 18 time point was performed to assess whether there was 1 (or more) subscales that was more influential on the primary endpoint outcome than the other subscale(s). Changes from Baseline at Month 18 for the 3 NIS-LL subscales (muscle weakness, reflexes, sensation) are demonstrated in Figure 4.

Table 6. NIS-LL Subscale Baseline Values (ITT Population)

NIS-LL Subscale		Tafamidis 20 mg N=64	Placebo N=61	p-Value
Muscle weakness (range 0-64)	Mean (SD)	2.9 (7.4)	4.2 (9.3)	
	Median	0.0	0.0	0.5131
	Range	0, 39	0, 39	
Reflexes (range 0-8)	Mean (SD)	1.2 (2.0)	1.7 (2.2)	
	Median	0.0	0.5	0.0931
	Range	0, 8	0, 8	
Sensation (range 0-16)	Mean (SD)	4.3 (3.4)	5.6 (3.8)	
	Median	4.0	5.0	0.0682
	Range	0, 14	0, 16	

ITT = intent-to-treat; N = evaluable number of subject; NIS-LL = neuropathy impairment score - lower limb; SD = standard deviation.

Figure 4. NIS-LL Subscale Scores LSMean (SE) Changes From Baseline to Month 18 (ITT Population, Observed Case)



p-values were based on a repeated measures ANOVA with change from Baseline as the dependent variable, an unstructured covariance matrix, treatment, month and treatment x month as fixed effects and subject as a random effect in the model.
Anova = analysis of variance; ITT = intent-to-treat; NIS-LL = neuropathy impairment score - lower limb; SE = standard error.

Similar to the rate of disease progression analysis that was performed for the NIS-LL total, an analysis of the rate of change over the course of the 18 month treatment period for each NIS-LL subscale was performed. The rate of disease progression, measured as the rate of change from Baseline in NIS-LL per month for each NIS-LL subscale, is summarized by treatment group in Table 7. Rates of worsening were numerically greater for the placebo group than for the tafamidis group for each of the 3 subscales. The greatest treatment benefit of tafamidis was observed for the rate of worsening in muscle weakness in comparison to placebo (p-value = 0.0164); the placebo group demonstrated an average rate of worsening in muscle weakness that was more than 3 times that of the tafamidis group.

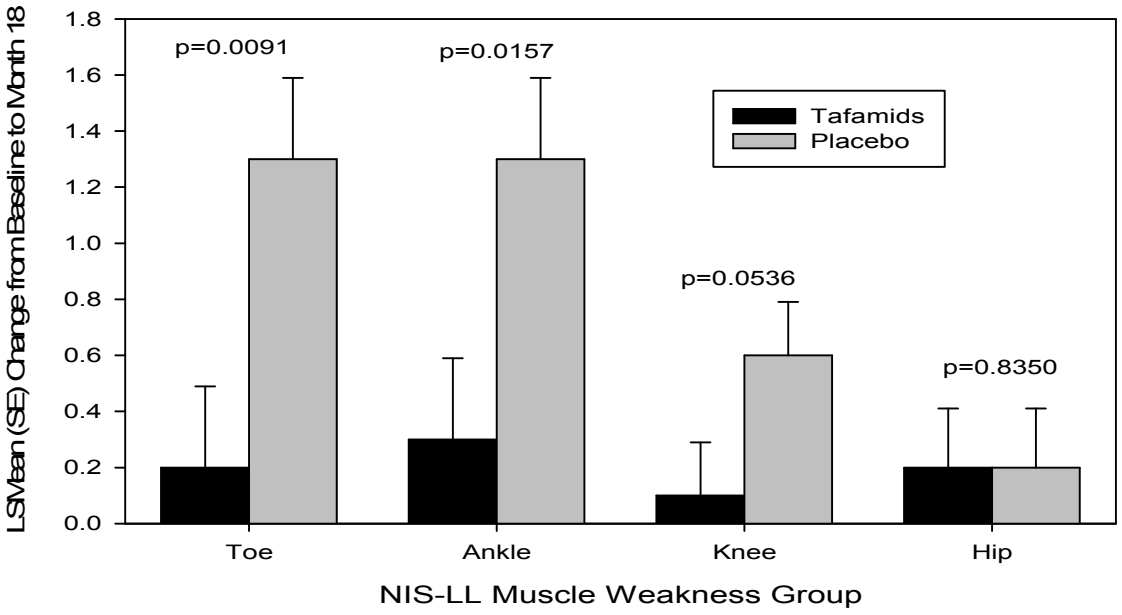
Table 7. Rate of Change in NIS-LL Subscales per Month (ITT Population)

	Tafamidis 20 mg	Placebo	Rate Difference (Tafamidis-Placebo)
Muscle weakness			
Units/month (SE)	0.057 (0.0409)	0.198 (0.0413)	-0.141 (0.058)
95% confidence interval			-0.256, -0.026
p-value			0.0164
Reflexes			
Units/month (SE)	0.031 (0.0089)	0.047 (0.0089)	-0.016 (0.013)
95% confidence interval			-0.041, 0.009
p-value			0.2156
Sensation			
Units/month (SE)	0.064 (0.0205)	0.097 (0.0206)	-0.033 (0.029)
95% confidence interval			-0.091, 0.024
p-value			0.2521

ITT = intent-to-treat; NIS-LL = neuropathy impairment score - lower limb; SE = standard error.

Furthermore exploration of the basis for the preservation of muscle strength in the tafamidis group was performed, to better understand which specific muscle groups contributed most significantly to this treatment effect. Assessments were performed for the toe, ankle, knee, and hip muscle groups. The results from the analysis of the specific muscle groups contributing to the muscle weakness subscale of the NIS-LL are provided in Figure 5. The results demonstrated a progression of muscle weakness in the placebo group in a distal to proximal fashion. There was a statistically significant treatment effect at 18 months in muscle weakness for the toe and ankle joints (p-values = 0.0091 and 0.0157, respectively) and numerical advantages for tafamidis-treated subjects in comparison to placebo-treated subjects for the knee joint. The hip did not demonstrate progression of muscle weakness in either group.

Figure 5. NIS-LL Muscle Weakness Subscale by Individual Muscle Groups Change From Baseline at Month 18 (ITT Population, Observed Case)



p-values were based on a repeated measures ANOVA with change from Baseline as the dependent variable, an unstructured covariance matrix, treatment, month and treatment x month as fixed effects and subject as a random effect in the model.
ANOVA = analysis of variance; ITT = intent-to-treat; LS = least square; NIS-LL = neuropathy impairment score - lower limb; SE = standard error.

Norfolk QOL-DN (TQOL): Higher scores on the Norfolk QOL-DN TQOL indicate worse quality of life; thus, increases from Baseline reflect a worsening in quality of life. Table 8 provides the primary efficacy assessment at Month 18 for the TQOL.

The placebo-treated subjects in the ITT population had progressively worse TQOL scores than tafamidis-treated subjects, but the differences between groups were not statistically significant (p-value = 0.1157). Furthermore, the changes from Baseline to Month 6 and to Month 12 were not significant. However, during the 18-month treatment period, the tafamidis group demonstrated advantages in the measurement of maintenance of quality of life compared to Baseline relative to the placebo group. Treatment effect differences became numerically evident by Month 12, with the treatment effect continuing to increase through Month 18.

Table 8. TQOL Change from Baseline to 18 Months – Co-Primary Endpoint Analysis (ITT Population, LOCF)

		Tafamidis 20 mg N=64	Placebo N=61	Tafamidis vs. Placebo
TQOL change from Baseline[a]	Mean (SD)	2.4 (14.6)	6.9 (22.9)	
	Median	1.0	6.0	
	Range	-36, 43	-74, 65	
	LSMean ± SE[b]	2.0 ± 2.3	7.2 ± 2.4	
	95% confidence interval[b]	-2.6, 6.6	2.6, 11.9	
	p-value[b]			0.1157

ANCOVA = analysis of covariance; ITT = intent-to-treat; LOCF = last observation carried forward; N = evaluable number of subject; SD = standard deviation; SE = standard error; TQOL = total quality of life.

a. LOCF was used to impute missing values at Month 18. For subjects without post-baseline TQOL values, the mean change from Baseline at 18 months for subjects with post-baseline assessments was used to impute the change from Baseline within each treatment group.

b. Based on ANCOVA model with baseline TQOL as covariate and effect of treatment in the model.

The rate of disease progression, measured as the rate of change from Baseline in TQOL per month, is summarized by treatment group in Table 9. Over the course of the 18 months of treatment, the average monthly rate of change in the TQOL for the placebo group was more than 3 times than that of the tafamidis group. This outcome was consistent with subjects in the tafamidis group more successfully maintaining quality of life over the course of the 18-month treatment period in comparison to subjects in the placebo group, with the rate of worsening of quality of life greater for the placebo group than for the tafamidis group.

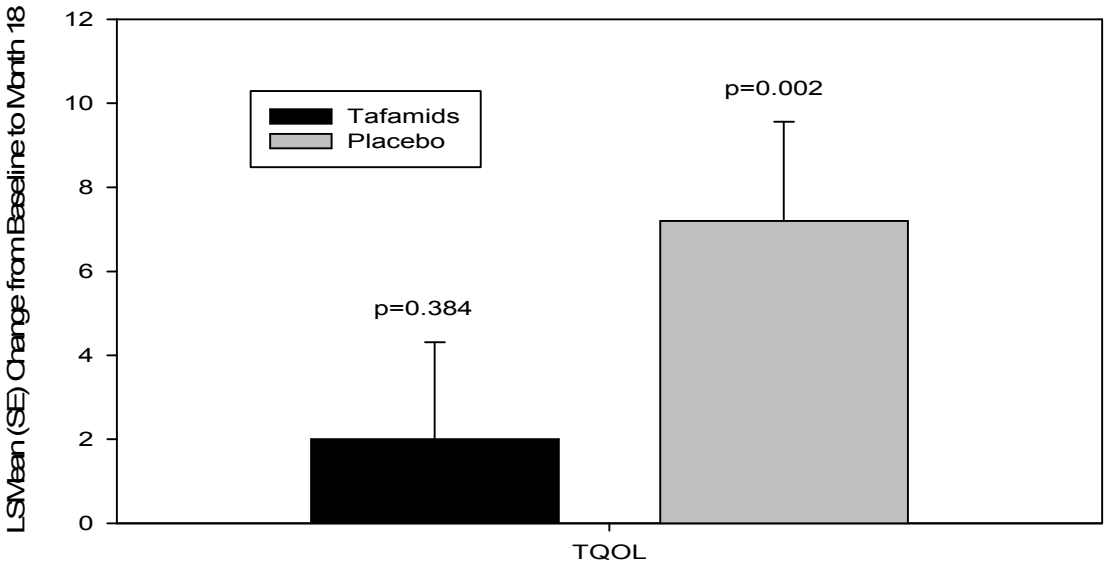
Table 9. TQOL Rate of Change per Month (ITT Population)

TQOL	Tafamidis 20 mg	Placebo	Rate Difference (Tafamidis - Placebo)
Units/month (SE)	0.1225 (0.1537)	0.4618 (0.1545)	-0.3392 (0.2179)
95% confidence interval			-0.7690, 0.09055
p-value			0.1212

ITT = intent-to-treat; SE = standard error; TQOL = total quality of life.

The within-treatment group changes from Baseline to Month 18 in the TQOL for the ITT population are demonstrated in Figure 6. While the TQOL changes from Baseline were not statistically significantly different between the treatment groups, there was a significant change from Baseline within the placebo group (p=0.002), reflecting a significant deterioration in quality of life over the 18 month treatment period; the changes from Baseline to Month 18 within the tafamidis group were not significant (p=0.384).

Figure 6. TQOL Within-Treatment Group LSMean (SE) Change From Baseline to Month 18 (ITT Population, LOCF)



LOCF was used to impute missing values at Month 18. For those subjects without post-baseline TQOL, the mean change from Baseline at Month 18 for subjects with post-baseline assessment was used to impute the change from Baseline within each treatment group.
p-values were based on an ANCOVA model with baseline TQOL as covariate and effect of treatment in the model. p-value indicates whether within treatment group change from Baseline is significantly different from 0.
ANCOVA = analysis of covariance; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least square; SE = standard error; TQOL = total quality of life.

The TQOL scores from the Norfolk QOL-DN at Month 18 are provided for the efficacy evaluable population in Table 10. The Efficacy population analysis for the TQOL demonstrates that the tafamidis group had both numerical and statistically significantly (p-value = 0.0454) better outcomes relating to changes in quality of life from Baseline to the primary time point (Month 18) than did the placebo group.

Table 10. TQOL Change from Baseline at 18 Months (Efficacy Evaluable Population)

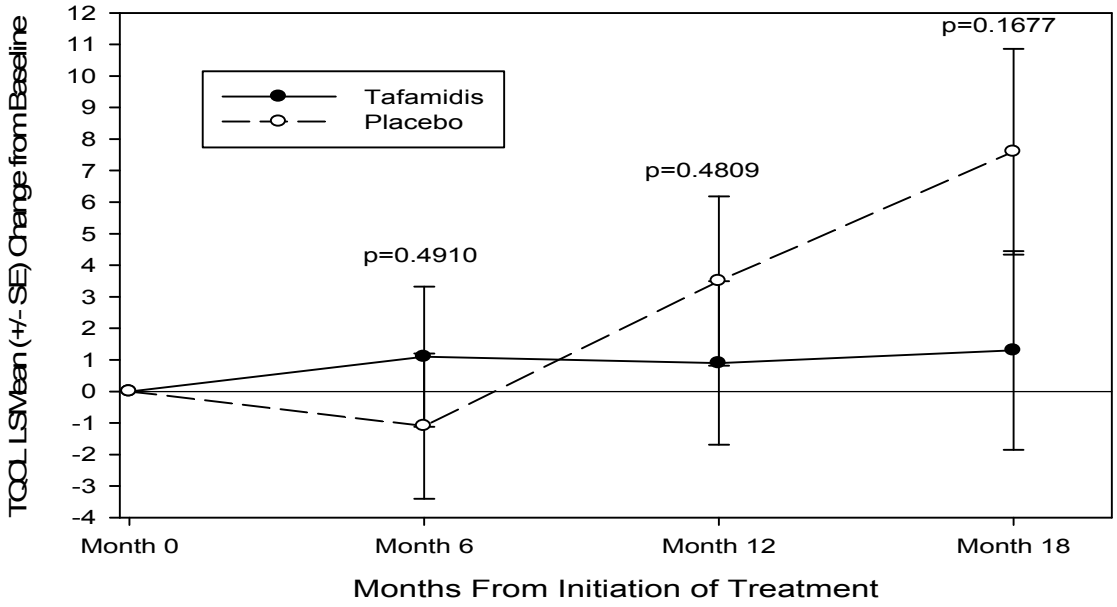
		Tafamidis 20 mg N=45	Placebo N=42	Tafamidis vs Placebo
TQOL change from Baseline[a]	Mean (SD)	1.3 (15.0)	7.6 (26.2)	
	Median	-1.0	5.0	
	Range	-36, 43	-74, 65	
	LSMean ± SE[b]	0.1 ± 3.0	8.9 ± 3.1	
	95% confidence interval[2]	-5.8, 6.0	2.8, 15.0	
	p-value[2]			0.0454

ANCOVA = analysis of covariance; LS = least square; LOCF = last observation carried forward; N = number of evaluable subjects; SD = standard deviation; TQOL = total quality of life.

a. LOCF was used to impute missing values at Month 18. For subjects without post-baseline TQOL values, the mean change from Baseline at 18 months for subjects with post-baseline assessments was used to impute the change from Baseline within each treatment group.
b. Based on ANCOVA model with baseline TQOL as covariate and effect of treatment in the model.

Figure 7 provides the analysis of the TQOL for the Efficacy population at each of the 3 on treatment time points. The analysis of the TQOL for the Efficacy Evaluable population resulted in consistent conclusions as for the primary analysis (using the ITT population), ie, the placebo-treated subjects in the efficacy evaluable population had progressively worse TQOL scores than tafamidis-treated subjects, but the differences between groups were not statistically significant at any time point (including the primary endpoint, Month 18). As was observed for the ITT population, during the 18-month treatment period the efficacy evaluable population analysis demonstrated an apparent maintenance of quality of life in the tafamidis group, with worsening of quality of life in the placebo group. Treatment effect differences became numerically evident by Month 12, with the treatment effect continuing to increase through Month 18.

Figure 7. TQOL LSMean (SE) Change From Baseline to On-Treatment Visits (Efficacy Evaluable Population)



LSMean = least square mean; SE = standard error; TQOL = total quality of life.

Secondary Efficacy Analyses:

The secondary efficacy analyses include assessments of composite scores (large fiber functioning, small fiber functioning, and clinical/neurophysiologic composite functioning), as well as assessments of changes in mBMI and TTR stabilization.

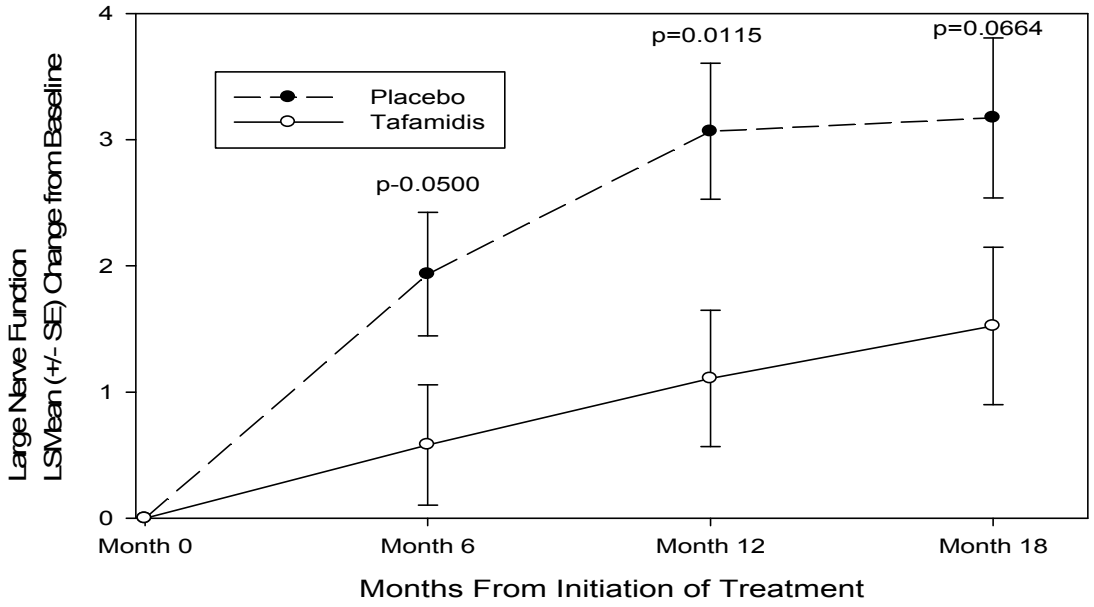
Large Fiber Function (Summated 7 Nerve Tests Normal Deviate Score [Σ7 NTs NDS]): Baseline large fiber function fiber values are shown in Table 11. The LSMean changes from Baseline to on-treatment time points for large fiber function are demonstrated in Figure 8. Treatment group differences in large fiber function became apparent as early as the 6-month study visit. The placebo group demonstrated numerically and statistically significantly greater loss in large fiber function than the tafamidis group at both Month 6 and Month 12 (and numerically greater loss at Month 18). Notably, the large fiber progression of disease at Month 18 for the tafamidis group was less than the progression of disease for the placebo group at Month 6, indicating that disease progression had slowed considerably for the tafamidis subjects.

Table 11. Baseline Large Fiber Functioning Values for Σ7 NTs NDS (ITT Population)

		Tafamidis 20 mg N=64	Placebo N=61	p-Value
Σ7 NTs NDS (range -26 to +26)	Mean (SD)	7.8 (9.1)	8.7 (8.5)	
	Median	7.4	9.7	0.5818
	Range	-13.6, 24.3	-10.6, 24.6	

Σ7 NTs NDS = Summated 7 nerve tests normal deviate score, ITT = intent-to-treat; N = number of evaluable subjects; SD = standard deviation.

Figure 8. Large Fiber Function LSMean (SE) Change From Baseline to On-Treatment Visits - Σ7 NTs NDS (ITT Population, Observed Case)



p-values were based on a repeated measures ANOVA with change from Baseline as the dependent variable, an unstructured covariance matrix, treatment, month and treatment x month as fixed effects and subject as a random effect in the model.

Σ7 NTs NDS = Summated 7 nerve tests normal deviate score; ANOVA = analysis of variance; ITT = intent-to-treat; LS = least square; SE = standard error.

The rate of disease progression, measured as the rate of change from Baseline in large fiber function per month, is summarized by treatment group in Table 12. The placebo group demonstrated an average worsening of large fiber function that was over twice that of the tafamidis group (0.1844 units/month for placebo compared to 0.08369 units/month for tafamidis); this difference was statistically significant (p-value = 0.0401). These outcomes indicate that worsening in large fiber function over 18 months was 55% slower in the tafamidis group than in the placebo group.

Table 12. Large Fiber Functioning Rate of Change - Σ7 NTs NDS per Month (ITT Population)

Σ7 NTs NDS	Tafamidis 20 mg	Placebo	Rate Difference (Tafamidis-Placebo)
Units/month (SE)	0.08369 (0.03439)	0.1844 (0.03452)	-0.1007 (0.04872)
95% confidence interval			-0.1968, -0.00462
p-value			0.0401

Σ7 NTs NDS = summated 7 nerve tests normal deviate score; ITT = intent-to-treat; SD = standard deviation; SE = standard error.

Small Fiber Function (Summated 3 Nerve Tests Small Fiber Normal Deviate Score [Σ3 NTSF NDS]): Baseline small fiber function values are shown in Table 13.

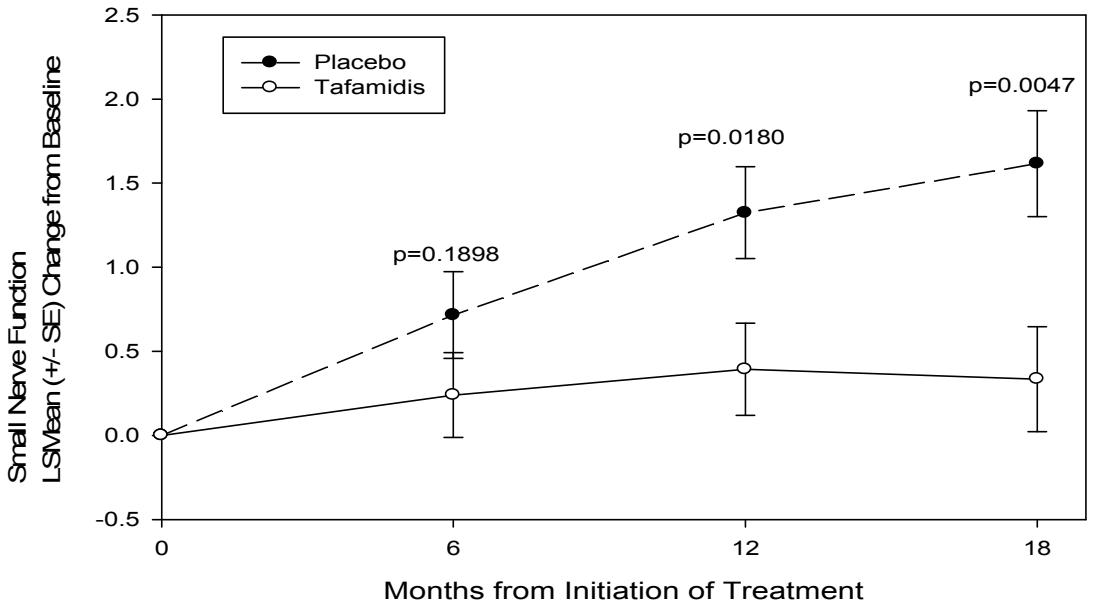
Table 13. Baseline Small Fiber Function Values for Σ3 NTSF NDS (ITT Population)

		Tafamidis 20 mg N=64	Placebo N=61	p-Value[a]
Σ3 NTSF NDS (range -11.2 to +11.2)	Mean (SD)	5.5 (4.5)	5.6 (4.1)	
	Median	4.8	5.0	0.9980
	Range	-4.5, 11.2	-3.7, 11.2	

Σ3 NTSF NDS = summated 3 nerve tests small fiber normal deviate score; ITT = intent-to-treat; N = number of evaluable subjects; SD = standard deviation.
a. p-value derived using Wilcoxon test.

The LSMean changes from Baseline to on-treatment time points for small fiber function are demonstrated in Figure 9. Treatment group differences in small fiber function became apparent as early as the 6-month study visit. The placebo group demonstrated numerically and statistically significantly greater loss in small fiber function than the tafamidis group at both Month 12 and Month 18 (and numerically greater loss at Month 6). Notably, the small fiber progression of disease at Month 18 for the tafamidis group was numerically less than the progression of disease for the placebo group at Month 6, indicating that disease progression had slowed considerably for the tafamidis subjects.

Figure 9. Small Fiber Function LSMean (SE) Change from Baseline to On-Treatment Visits - Σ3 NTSF NDS Over Time (ITT Population, Observed Case)



p-values were based on a repeated measures ANOVA with change from Baseline as the dependent variable, an unstructured covariance matrix, treatment, month and treatment x month as fixed effects and subject as a random effect in the model.
Σ3 NTSF NDS = summated 3 nerve tests small fiber normal deviate score; ANOVA = analysis of variance; ITT = intent-to-treat; LS = least square; SE = standard error.

The rate of disease progression, measured as the rate of change from Baseline in small fiber function per month, is summarized by treatment group in Table 14. The placebo group demonstrated an average worsening of small fiber function that was 6 times that of the tafamidis group (0.0926 units/month for placebo compared to 0.01505 units/month for tafamidis); this difference was statistically significant (p-value = 0.0022). These outcomes indicate that worsening in small fiber function over 18 months was 84% slower in the tafamidis group than in the placebo group.

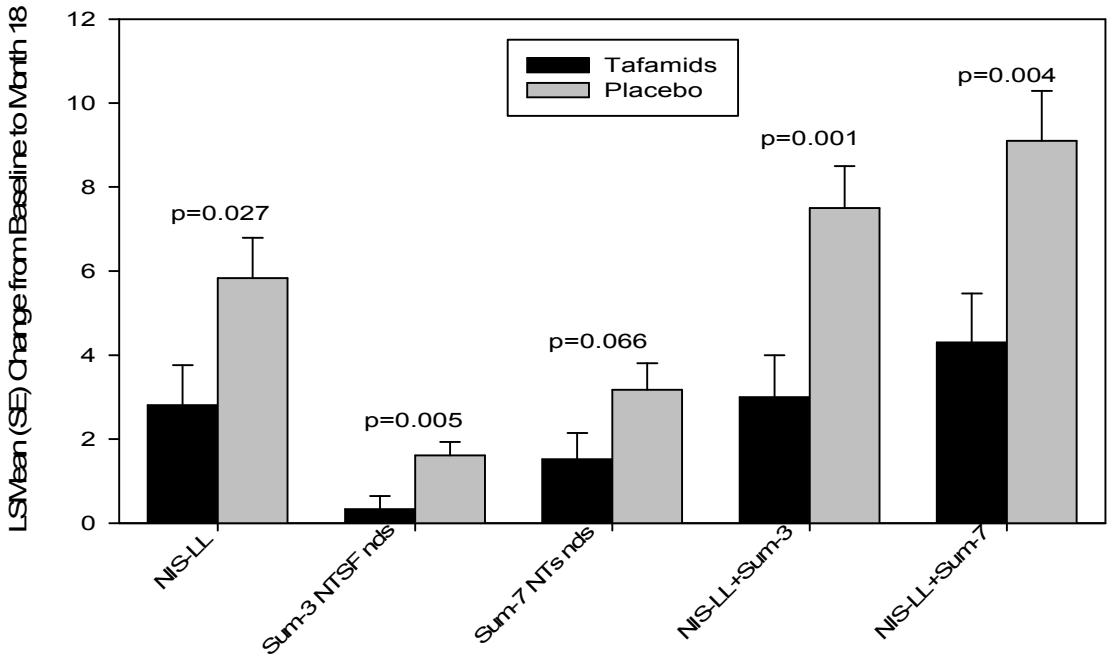
Table 14. Small Fiber Function Rate of Change - Σ3 NTSF NDS per Month (ITT Population)

Σ3 NTSF NDS	Tafamidis 20 mg	Placebo	Rate Difference (Tafamidis - Placebo)
Units/month (SE)	0.01505 (0.01760)	0.09260 (0.01767)	-0.07755 (0.02494)
95% confidence interval			-0.1267, -0.02836
p-value			0.0022

Σ3 NTSF NDS = summated 3 nerve tests small fiber normal deviate score; ITT = intent-to-treat; N = number of evaluable subjects; SE = standard error.

NIS-LL+Σ3 and NIS-LL+Σ7: NIS-LL+Σ3 combines the NIS-LL and the Σ3 NTSF NDS (lower limbs) for each subject. NIS-LL+Σ7 combines the NIS-LL and the Σ7 NTs NDS (lower limbs) for each subject. Figure 10 displays the change from Baseline at 18 months in the clinical/neurophysiological composite as well as for the individual components (NIS-LL, small fiber [Σ3 NTSF NDS], and large fiber [Σ7 NTs NDS]) by treatment group. There were statistically significant differences between the treatment groups for each composite (NIS-LL+Σ3: p=0.001; NIS-LL+Σ7: p=0.004), with the placebo group demonstrating significant worsening in these clinical/neurophysiologic scores when compared to the tafamidis group.

Figure 10. Change from Baseline at 18 Months in All Composite Scores (ITT Population)

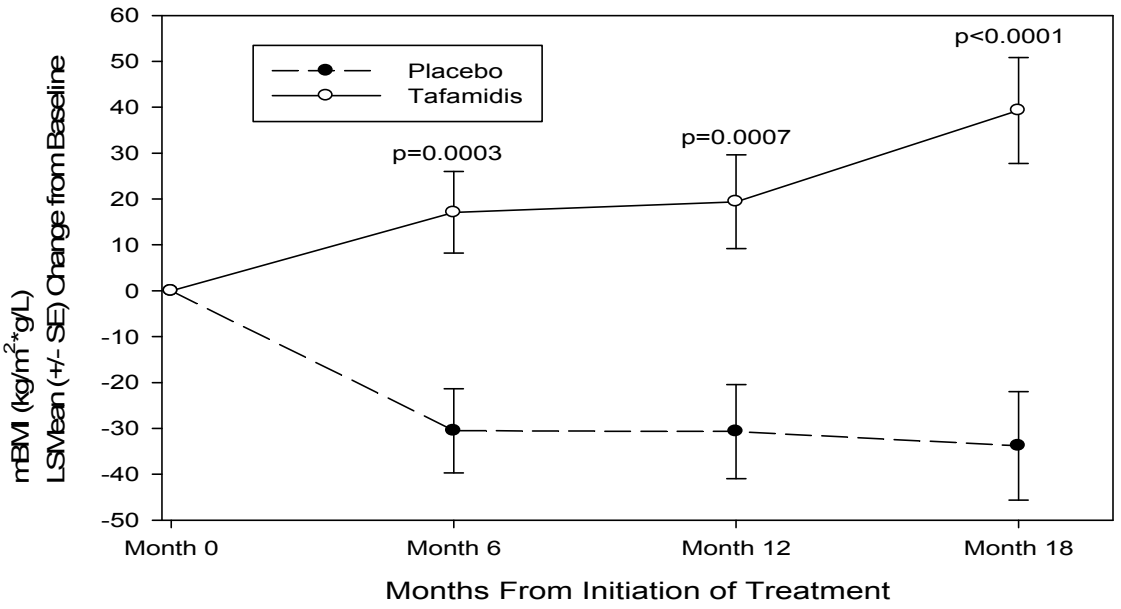


ITT = intent-to-treat; LSmean = least square mean; NDS = normal deviate score; NIS-LL = neuropathy impairment score - lower limb; SE = standard error.

Modified Body Mass Index: The mBMI was used to assess the nutritional status of subjects in this study. The mBMI was more appropriate than BMI, as mBMI includes a correction for the effect of edema due to low serum albumin level on BMI (mBMI = serum albumin [g/L] × BMI [kg/height in m^2]). Average pre-treatment mBMI was similar between the treatment groups (tafamidis mean = 1004 [SD = 165.2] and placebo mean = 1011 [SD = 212.9]). The change from Baseline in mBMI at Months 6, 12, and 18 is shown for the ITT population in Figure 11. Over the course of the 18-month treatment period, subjects treated with placebo experienced an average reduction in their mBMI at each on-treatment study visit; in contrast, subjects treated with tafamidis experienced an average increase in their mBMI at each on-treatment study visit (by 18 months, there was a

73.1-point difference between the tafamidis (LSMean [±SE] change from Baseline of 39.3±11.5) and placebo (-33.8 ± 11.8) groups (p value <0.0001).

Figure 11. mBMI LSMean (SE) Change From Baseline to On-Treatment Time Points (ITT Population, Observed Case)



p-values were based on a repeated measures ANOVA with change from Baseline as the dependent variable, an unstructured covariance matrix, treatment, month and treatment x month as fixed effects and subject as a random effect in the model.
ANOVA = analysis of variance; ITT = intent-to-treat; LS = least square; mBMI = modified body mass index; NIS-LL = neuropathy impairment score - lower limb; NTSF NDS = summated 3 nerve tests small fiber normal deviate score; SE = standard error.

Baseline albumin levels were in the normal range in both groups (4.4 and 4.3, respectively, for the tafamidis and placebo groups). At Month 18, a slight increase (0.1 ± 0.31) in mean albumin relative to baseline was observed in the tafamidis group and no change (0.0 ± 0.37) was observed in the placebo group. Absolute values at Month 18 were within the normal range for both groups.

Taken together, these findings indicate that the changes in mBMI were due to alterations in both body weight and serum albumin.

The rate of disease progression, measured as the rate of change from Baseline in mBMI per month, is summarized by treatment group in Table 15. The placebo group demonstrated an average worsening in mBMI while the tafamidis group demonstrated an average improvement in mBMI; these differences between the treatment groups were statistically significant (p-value <0.0001). Placebo-treated TTR-FAP subjects in this study exhibited greater disease progression via lower mBMI than did tafamidis-treated TTR-FAP subjects.

Table 15. Rate of Change in mBMI per Month (ITT Population)

mBMI	Tafamidis 20 mg	Placebo	Rate Difference (Tafamidis - Placebo)
Units/month (SE)	2.0451 (0.6094)	-1.6240 (0.6157)	3.6691 (0.8663)
95% confidence interval			1.9604, 5.3777
p-value			<0.0001

mBMI = modified body mass index.

TTR Stabilization: TTR stabilization results are summarized in Table 16. TTR stabilization (as defined by the TTR stabilization assay) was observed in 97.9% of subjects on tafamidis and no subjects on placebo at 18 months. A logistic regression analysis of stabilization status at Week 8 (yes = stabilized; no = not stabilized) and NIS-LL responder status at the primary time point (Month 18) yielded an odds ratio of 2.053 (p=0.0738).

Table 16. TTR Stabilization Status (ITT Population)

		Tafamidis 20 mg N=64	Placebo N=61	Tafamidis vs Placebo
Week 8	Stabilized/observations (%)	62/63 (98.4)	4/60 (6.7)	
	95% confidence interval	95.3%, 100%	0.4%, 13.0%	
	p-value[a]			<0.0001
Month 6	Stabilized/observations (%)	59/59 (100)	3/58 (5.2)	
	95% confidence interval	100%, 100%	0.0%, 10.9%	
	p-value[a]			<0.0001
Month 12	Stabilized/observations (%)	47/48 (97.9)	1/50 (2.0)	
	95% confidence interval	93.9%, 100%	0.0%, 5.9%	
	p-value[a]			<0.0001
Month 18	Stabilized/observations (%)	47/48 (97.9)	0/44 (0.0)	
	95% confidence interval	93.9%, 100%	0.0%, 0.0%	
	p-value[a]			<0.0001

ITT = intent-to-treat; N = number of evaluable subjects.
a. Based on Chi-square test for proportions.

TTR stabilization was not observed in 1 subject in the tafamidis group. This subject did not have measureable concentrations of plasma tafamidis at Months 12 and 18, suggesting that the subject was not compliant with the dosing regimen.

The relationship between TTR stabilization at Week 8 and clinical outcomes (NIS-LL and TQOL) at Months 6, 12 and 18 was also examined. The results for both endpoints at Month 18 are shown in Table 17. Note that this analysis used pooled data across the 2 treatment groups; the comparison here was based on TTR stabilization status.

There were a total of 66 subjects with stabilized TTR at Week 8 (62 tafamidis subjects, 4 placebo subjects). Subjects without stabilized TTR at Week 8 had a statistically significant worsening of neurologic impairment at Month 12 (p=0.0052) and Month 18 (p=0.0152) compared with the subjects with stabilized TTR. TQOL change from Baseline values indicated worsening of quality of life in subjects without stabilized TTR at Week 8, while there was little change in subjects who had stabilized TTR. However, there were no statistically significant differences between these groups at any time point.

Table 17. NIS-LL and TQOL Change From Baseline at 18 Months by TTR Stabilization Status at Week 8 (ITT Population)

		TTR Stabilized N=66	TTR Not Stabilized N=57	Stabilized vs Not Stabilized
NIS-LL change from Baseline	n	50	44	
	Mean (SD)	2.3 (4.4)	5.5 (8.9)	
	Median	1.0	3.2	
	Range	-4.5, 19.8	-6.0, 42.0	
	LSMean ± SE[a]	2.8 ± 0.9	6.1 ± 1.0	
	95% confidence interval[a]	0.9, 4.6	4.1, 8.1	
	p-value[a]			0.0152
TQOL change from Baseline	n	50	44	
	Mean (SD)	2.2 (17.1)	7.1 (23.9)	
	Median	-0.5	3.5	
	Range	-36, 54	-74, 65	
	LSMean ± SE[a]	2.5 ± 2.8	8.2 ± 3.0	
	95% confidence interval[a]	-3.1, 8.0	2.3, 14.1	
	p-value[a]			0.1607

ITT = intent-to-treat; n = number of subject with the observation; N = number of evaluable subjects; NIS-LL = neuropathy impairment score - lower limb; SD = standard deviation; SE = standard error; TQOL = total quality of life; TTR = transthyretin.

a. Based on repeated measures ANOVA with change from Baseline as the dependent variable; an unstructured covariance matrix; TTR stabilization at Week 8, month, and TTR stabilization at Week 8 by month interaction as fixed effects; and subject as a random effect.

The analyses of the co-primary endpoints in stabilized and non-stabilized subjects were consistent with the results in tafamidis and placebo subjects and reflect the strong association between active and placebo treatment and TTR stabilization. Stabilization of TTR was significantly predictive of slowing of disease progression in subjects with TTR-FAP.

Safety Results:

The type and incidence of AEs in this study was not unexpected for a sample of subjects with TTR-FAP. A total of 863 AEs were reported by 121 (95%) of the 128 subjects: 392 in 60 (92%) tafamidis-treated subjects and 471 in 61 (97%) placebo-treated subjects. Thirty-nine (60%) tafamidis-treated subjects and 43 (68%) placebo-treated subjects reported at least 1 TEAE that was considered at least possibly related to study medication.

The most common treatment-related AEs included urinary tract infection, pain in extremity and headache and events in gastrointestinal system, eg, diarrhea, upper abdominal pain, nausea, vomiting and constipation. The placebo-treated subjects tended to have a higher incidence of events relating to TTR-FAP disease progression, eg, neuralgia, muscle spasm, peripheral edema, fatigue and paresthesia.

Treatment-emergent AEs (TEAEs) occurred in >5% subjects in either treatment group is presented in Table 18.

Table 18. Summary of Treatment-Emergent Adverse Events (>5% in Either Treatment Group) – Safety Population

Preferred Term	Tafamidis 20 mg N=65 n (%)	Placebo N=63 n (%)
Subjects with at least 1 non-serious AE	57 (87.7%)	56 (88.9%)
Anaemia	0 (0.0%)	4 (6.3%)
Atrioventricular block first degree	2 (3.1%)	6 (9.5%)
Vertigo	3 (4.6%)	4 (6.3%)
Lacrimation decreased	6 (9.2%)	7 (11.1%)
Punctate keratitis	5 (7.7%)	3 (4.8%)
Diarrhoea	17 (26.2%)	11 (17.5%)
Nausea	8 (12.3%)	8 (12.7%)
Vomiting	7 (10.8%)	7 (11.1%)
Constipation	4 (6.2%)	7 (11.1%)
Abdominal pain upper	8 (12.3%)	2 (3.2%)
Abdominal pain	3 (4.6%)	5 (7.9%)
Oedema peripheral	4 (6.2%)	8 (12.7%)
Fatigue	0 (0.0%)	6 (9.5%)
Urinary tract infection	14 (21.5%)	8 (12.7%)
Influenza	10 (15.4%)	9 (14.3%)
Nasopharyngitis	9 (13.8%)	8 (12.7%)
Pharyngitis	4 (6.2%)	5 (7.9%)
Upper respiratory tract infection	4 (6.2%)	3 (4.8%)
Vaginal infection	4 (6.2%)	1 (1.6%)
Thermal burn	4 (6.2%)	5 (7.9%)
Weight decreased	3 (4.6%)	5 (7.9%)
Pain in extremity	11 (16.9%)	6 (9.5%)
Back pain	5 (7.7%)	4 (6.3%)
Muscle spasms	2 (3.1%)	7 (11.1%)
Myalgia	5 (7.7%)	2 (3.2%)
Headache	10 (15.4%)	12 (19.0%)
Neuralgia	2 (3.1%)	12 (19.0%)
Paraesthesia	3 (4.6%)	10 (15.9%)
Dizziness	2 (3.1%)	4 (6.3%)
Hypoaesthesia	1 (1.5%)	4 (6.3%)
Anxiety	4 (6.2%)	3 (4.8%)
Depression	4 (6.2%)	3 (4.8%)
Erectile dysfunction	4 (6.2%)	4 (6.3%)
Pharyngolaryngeal pain	2 (3.1%)	7 (11.1%)

Note: All AEs were coded using MedDRA dictionary Version 10.0. A subject with multiple events per system organ class or preferred term was counted only once per system organ class when counting subjects. The value following the percent of subjects was the number of events.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of evaluable subjects; n = number of subjects with adverse events.

Treatment related TEAEs occurred in >5% subjects in either treatment group is presented in Table 19.

Table 19. Summary of Treatment-Emergent Adverse Events (>5% in Either Treatment Group) – Safety Population (Treatment Related)

Preferred Term	Tafamidis 20 mg N=65 n (%)	Placebo N=63 n (%)
Number of subjects with at least 1 related AE	39 (60.0)	43 (68.3)
Urinary tract infection	7 (10.8)	0
Diarrhea	6 (9.2)	7 (11.1)
Upper abdominal pain	5 (7.7)	2 (3.2)
Pain in extremity	5 (7.7)	3 (4.8)
Headache	5 (7.7)	10 (15.9)
Nausea	4 (6.2)	6 (9.5)
Vomiting	3 (4.6)	5 (7.9)
Constipation	1 (1.5)	4 (6.3)
Neuralgia	1 (1.5)	7 (11.1)
Muscle spasms	1 (1.5)	5 (7.9)
Peripheral edema	1 (1.5)	5 (7.9)
Fatigue	0 (0.0)	5 (7.9)
Paresthesia	0 (0.0)	6 (9.5)

Adverse events coded using MedDRA v.10.
AEs and SAEs are not separated.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of evaluable subjects; n = number of subjects with adverse events; SAE = serious adverse event; v = version.

A summary of the incidence of serious TEAEs, sorted by descending incidence in the tafamidis group, is presented in Table 20.

Table 20. Summary of Serious Treatment-Emergent Adverse Events – Safety Population

Preferred Term	Tafamidis 20 mg N=65 n (%)	Placebo N=63 n (%)
Number of subjects with ≥1 SAE	6 (9.2)	5 (7.9)
Urinary tract infection	2 (3.1)	0 (0.0)
Conduction disorder	1 (1.5)	0 (0.0)
Localized infection	1 (1.5)	0 (0.0)
Pneumonia	1 (1.5)	0 (0.0)
Viral infection	1 (1.5)	0 (0.0)
Urticaria	1 (1.5)	0 (0.0)
Anaemia	0 (0.0)	1 (1.6)
Cardiac amyloidosis	0 (0.0)	1 (1.6)
Nausea	0 (0.0)	1 (1.6)
Vomiting	0 (0.0)	1 (1.6)
Catheter site phlebitis	0 (0.0)	1 (1.6)
Oedema peripheral	0 (0.0)	1 (1.6)
Cellulitis	0 (0.0)	1 (1.6)
Lymphangitis	0 (0.0)	1 (1.6)
Staphylococcal infection	0 (0.0)	1 (1.6)
Burns third degree	0 (0.0)	1 (1.6)
Syncope	0 (0.0)	1 (1.6)
Pneumothorax	0 (0.0)	1 (1.6)
Hypertensive emergency	0 (0.0)	1 (1.6)
Skin ulcer	0 (0.0)	1 (1.6)

One subject in tafamidis group experienced an SAE of hepatic artery thrombosis after completing study and after undergoing liver transplantation. This SAE was incorrectly captured as a treatment-emergent SAE in the clinical database but had been removed from the table above. The liver transplant for this subject was captured in the clinical database. All AEs coded using MedDRA v.10.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of evaluable subjects; n = number of subjects with adverse events; SAE = serious adverse event; v = version.

Other significant AEs were defined as events occurring post-liver transplant. A total of 26 (20%) of subjects (13 subjects in each treatment group) discontinued due to liver transplantation. Of the 26 transplanted subjects, 8 (30.8%) reported AEs post-liver transplant: 5 (38.5%) of 13 tafamidis-treated subjects and 3 (23.1%) placebo-treated subjects. Table 21 presents a summary of the SAEs reported post-liver transplantation.

Table 21. Serious Adverse Events Occurring Post-Liver Transplantation – Safety Population

Serial No.	Treatment Group	MedDRA Preferred Term	Relationship to Study Medication
1	Tafamidis	Cardiac tamponade	Unrelated
2[a]	Tafamidis	Hepatic artery thrombosis	Possibly
3	Tafamidis	Bile duct stenosis	Unrelated
4	Placebo	Hepatic failure	Unrelated
5	Placebo	Encephalitis	Unrelated
		Autonomic nervous system imbalance	Unrelated
		Sepsis	Unrelated

Adverse events coded using MedDRA v.10.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; v = version.
a. One subject in tafamidis group experienced hepatic artery thrombosis after completing study and after undergoing liver transplantation after enrolling into study. This SAE was incorrectly captured as a treatment-emergent SAE in the clinical database and had been included in this table as occurring post-transplant.

A total of 4 subjects deaths occurred in this study, all of which followed liver transplantation; no deaths occurred during study participation or prior to liver transplantation. Of note, 1 subject death was not included in the clinical database. This placebo subjects discontinued the study after approximately 11 months in the study to undergo liver transplant. This subject died 10 days after transplantation but her death was not reported as an SAE until after clinical database lock. Table 22 is by-subject summary for the 4 subjects who died following liver transplantation.

Table 22. Listing of Subject Deaths – Safety Population

Serial No.	Treatment Group	MedDRA Preferred Term	Relationship to Study Medication as Judged by the Investigator
1	Tafamidis	Cardiac tamponade	Unrelated
2	Placebo	Hepatic failure	Unrelated
3	Placebo	Sepsis	Unrelated
4	Placebo	Unknown (post-transplant)[a]	Unrelated

Adverse events coded using MedDRA v.10
MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. One subject died 10 days post-transplant after approximately 11 months in the study. No details of this death were available and this death did not appear in the clinical database as it was not reported as an SAE until after clinical database lock.

Subjects having liver transplant were discontinued from study medication prior to the transplant procedure, and thus the deaths occurred after subjects had already been discontinued from study medication. One subject, treated with tafamidis prior to liver transplant, died due to cardiac tamponade (pacemaker insertion complication). Three subjects treated with placebo prior to liver transplant died, 1 due to hepatic failure post-transplant, 1 due to sepsis post-transplant and 1 unknown cause. All 4 subject deaths were assessed to be not related to study medication.

Table 23 is a summary of TEAEs that led to study discontinuation. A total of 7 (5.5%) subjects experienced a total of 9 TEAEs that led to study discontinuation, 4 TEAEs in

4 tafamidis-treated subjects and 5 TEAEs in 3 placebo-treated subjects. Twenty-six (20.3%) subjects (13 in each treatment group) discontinued the study due to liver transplant.

Table 23. Subjects Who Discontinued Due to a Treatment-Emergent Adverse Event - Safety Population

Serial No.	Treatment Group	Adverse Event
1	Tafamidis	Diarrhea
2	Tafamidis	Nausea
3	Tafamidis	Urticaria[a]
4	Tafamidis	Pregnancy (outcome normal)
5	Placebo	Paresthesia, fatigue
6	Placebo	Nausea, Unintentional weight loss
7	Placebo	Worsening cardiac amyloidosis[a]

a. Serious adverse event.

CONCLUSION: The efficacy and safety analyses for this study were well-defined and implemented; primary outcomes were supported with numerous sensitivity, subpopulation, and robustness analyses. Results, which were consistent across all variables and methods of analysis, demonstrated that tafamidis significantly halted and/or slowed disease progression in subjects with TTR-FAP. TTR stabilization results further support the scientific hypothesis that prevention of TTR tetramer dissociation by the pharmacological chaperone tafamidis results in less deterioration of neurophysiological function, which results in less neurologic impairment, ultimately translating to maintenance of quality of life and reduced burden of disease. Treatment during 18 months resulted in an acceptable safety and tolerability profile. The benefits of tafamidis treatment in the study population were evident, and the potential risks associated with treatment were minimal.

The outcomes from this study have demonstrated that once-daily dosing with 20 mg tafamidis is an effective and well-tolerated disease-modifying treatment for subjects living with TTR-FAP.