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

PROTOCOL NO.: Fx1A-201 (B3461022)

PROTOCOL TITLE: The Effects of Fx-1006A on Transthyretin Stabilization and Clinical Outcome Measures in Patients With Non-V30M Transthyretin Amyloidosis

Study Centers: Four (4) centers took part in the study and enrolled subjects; 1 each in France, Germany, Italy and the United States.

Study Initiation and Final Completion Dates: 12 June 2008 to 26 January 2010

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To determine transthyretin (TTR) stabilization at steady-state, as measured by a validated immunoturbidimetric stabilization assay in subjects with non-valine replaced by methionine at position 30 (V30M) TTR amyloidosis.

Secondary Objectives:

- To evaluate the safety and tolerability of tafamidis in subjects with non-V30M TTR amyloidosis;
- To determine plasma concentrations at selected steady-state time points;
- To evaluate clinical outcomes in subjects with non-V30M TTR amyloidosis.

METHODS

Study Design: This was an open-label, multicenter, international study. The study was designed to determine TTR stabilization as well as tafamidis safety and tolerability, and its effects on clinical outcomes in subjects with non-V30M TTR amyloidosis. The study was conducted in 2 parts. Part 1 included a 6-week dosing period during which all enrolled subjects received oral tafamidis 20-mg soft gelatin capsules once daily for 6 weeks. At Week 6, blood samples were collected from each subject to determine TTR stabilization. Subjects who completed the Week 6 Visit continued receiving daily oral tafamidis 20 mg for up to a total of 12 months during Part 2 of the study. As planned in the protocol, if it was

determined that a subject was not stabilized at Week 6, the subject was to be discontinued from the study. Table 1 presents the schedule of events for all study visits.

Table 1. Schedule of Events

	Screen 1 Days -30 to -1	Screen 2 Days -7 to 0	Day 0 Visit	Day 1	2 Wk Visit ± 2 Days	6 Wk Visit ± 1 Wk	3 Mo Visit ± 2 Wks	6 Mo Visit ± 2 Wks	12 Mo Visit ± 2 Wks	Follow-Up Contact[a]
Informed consent	X									
Medical history/demographics[b]	X									
Review of entrance criteria	X		X							
Biopsy to confirm amyloid[c]	X									
Physical examination	X								X	
Abbreviated physical examination					X	X	X	X		
Body weight	X							X	X	
Body height	X									
12-Lead ECG	X		X		X	X	X	X	X	
Vital signs	X		X		X	X	X	X	X	
Serology[d]	X									
Saliva sample for TTR sequencing			X							
Urine pregnancy test (females of child-bearing potential only)	X		X		X	X	X	X	X	
Laboratory tests (hematology, coagulation panel, serum chemistry, and urinalysis)	X		X		X	X	X	X	X	
Enrollment			X							
NIS (including NIS-LL and NIS-UL)[e]		X	X					X	X	
Norfolk QOL-DN			X					X	X	
NCS			X					X	X	
HRDB			X					X	X	
SF-36			X					X	X	
Karnofsky score			X					X	X	
NT-pro-BNP and troponin I			X		X	X	X	X	X	
Echocardiography			X					X	X	
24-hour Holter monitoring			X					X	X	

Table 1. Schedule of Events

	Screen 1 Days -30 to -1	Screen 2 Days -7 to 0	Day 0 Visit	Day 1	2 Wk Visit ± 2 Days	6 Wk Visit ± 1 Wk	3 Mo Visit ± 2 Wks	6 Mo Visit ± 2 Wks	12 Mo Visit ± 2 Wks	Follow-Up Contact[a]
Study medication compliance					X	X	X	X	X	
Study medication dispensation[f]			X		X	X	X	X		
First study medication dose				X						
Blood sample for PK analysis[g]			X			X		X	X	
Blood sample for TTR stabilization assay			X			X		X	X	
Adverse events[h]		X	X		X	X	X	X	X	X
Concomitant medications[h]	X	X	X		X	X	X	X		X

ATTR-PN = transthyretin amyloidosis with polyneuropathy; ECG = electrocardiogram; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRDB = heart rate response to deep breathing; LL = lower limb; Mo = month; NCS = nerve conduction studies; NT-pro-BNP = N-terminal pro-hormone brain natriuretic peptide; NIS = Neuropathy Impairment Score; PK = pharmacokinetic. QOL-DN = Quality of Life-Diabetic Neuropathy; SF-36 = SF-36 Quality of Life Questionnaire; TTR = transthyretin; UL = upper limb; Wk = week.

a. Additional information was recorded regarding subject's ATTR-PN symptoms, including age at onset of symptoms, history of Carpal Tunnel Syndrome, etc.
b. Biopsy was performed within 5 years of enrollment. If greater than 5 years, biopsy was repeated at the investigative site.
c. All subjects were tested for HbsAg, anti-HCV, and HIV during the screening period only.
d. NIS testing was performed 2 times at least 24 hours apart within a 1-week period. At Baseline, both evaluations were completed prior to study medication administration. All NIS testing was conducted by the same neurologist at the clinical site throughout the study.
e. Months 10 through 12 study medication supply was shipped to the subject's home at Month 9.
f. Two blood samples for measurement of tafamidis levels were collected from each subject at Week 6 and Months 6 and 12, with the first sample collected as soon as the subject arrived at the clinical site (but after Norfolk QOL-DN testing), and the second sample collected immediately prior to the subject leaving the site, after all other scheduled procedures were completed for the visit.
g. Monthly telephone contact (± 1 week of the scheduled date) at non-clinical visit months to monitor for adverse events and concurrent medications including a final telephone contact 30 days after the last study medication dose.
h. A follow-up telephone contact was made for each subject 30 days after administration of the last dose of study medication.

Number of Subjects (Planned and Analyzed): Up to 24 subjects were planned to be enrolled in this study. A total of 21 subjects (10 in the United States, 5 in France; 4 in Germany and 2 in Italy) were enrolled and analyzed.

Diagnosis and Main Criteria for Inclusion: Male and female subjects between the ages of 18 and 75 years inclusive diagnosed with TTR amyloidosis with documented non-V30M TTR mutation and positive biopsy, peripheral and/or autonomic neuropathy and/or cardiomyopathy with a Karnofsky Performance Status ≥50 were eligible for the study. Exclusion Criteria: Subjects who had undergone liver transplantation, who had positive results for hepatitis B surface antigen, anti-hepatitis C virus, and/or human immunodeficiency virus, renal insufficiency, liver function test abnormalities were not eligible for enrollment.

Study Treatment: All enrolled subjects received a once daily oral dose of tafamidis 20 mg in a soft gelatin capsule formulation for 12 months.

Tafamidis was supplied by the Sponsor as soft gelatin capsules filled with a suspension containing 20 mg of tafamidis. Study medication was supplied in 10-count child resistant blisterpacks.

Pharmacodynamic and Safety Endpoints:

Primary Endpoint: The primary endpoint of this study was TTR stabilization at Week 6 compared with Baseline, as measured by a validated immunoturbidimetric assay.

Secondary Endpoint: The secondary endpoint of this study was TTR stabilization at Months 6 and 12 compared with Baseline, as measured by a validated immunoturbidemetric assay.

Safety endpoints of this study were:

- Incidence of subjects experiencing treatment-emergent adverse events (TEAEs);
- Incidence of subjects experiencing treatment-emergent ≥Grade 3 adverse events;
- 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 with treatment-emergent Holter monitoring findings considered by the Investigator to be clinically significant;
- Incidence of subjects discontinuing from the study because of clinical or laboratory adverse events.

Safety Evaluations: All safety analyses were performed on the safety population, which comprised all enrolled subjects who received at least 1 dose of study medication. Safety analysis comprised of occurrence of AEs, TEAEs, vital signs, 12-lead ECG findings and echocardiogram assessments, Holter monitoring, clinical laboratory assessments, concomitant medications, and physical examination.

Statistical Methods:

Analysis Population:

Intent-to-Treat (ITT) Population: It consisted of all enrolled subjects who received at least 1 dose of study drug; therefore, the ITT and Safety populations for this study were the same. This population was used in all summaries.
The statistical analyses were performed at the end of Part 1 (ie, after 6 weeks of treatment) and at the end Part 2 (ie, after 12 months of treatment). At the end of Part 1, all pharmacodynamic, PK, and safety endpoints up to and including the Week 6 Visit were summarized. At the end of Part 2, data from Part 1 and Part 2 for all continuously collected data (ie, AEs, concomitant medication, and treatment compliance) were combined and summarized; all other endpoints were summarized by time point.

Primary Pharmacodynamic Analysis:
Part 1: TTR stabilization was measured at Day 0 and Week 6. The number, proportion and the 95% confidence intervals (CIs) for the proportion of subjects who achieved TTR stabilization were calculated. The Week 6 stabilization was the primary outcome for this study.
Part 2: In addition to Part 1, TTR stabilization was measured at Months 6 and 12. The number, proportion of TTR stabilization and the 95% confidence intervals were calculated at each time point. The 95% CI of the proportion of subjects stabilized was calculated using the exact binomial method for the ITT population.

Safety Analysis: Descriptive statistics of AE rates and all other safety measures were calculated and presented by study part; no hypothesis testing was performed on the safety data. Select ECG and echocardiography parameters were also classified as abnormal/normal. These parameters were summarized over time using counts and percentages.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 2 for all enrolled subjects.

Table 2. Subject Disposition – All Enrolled Subjects

	N=21 n (%)
Subjects screened	21
Screen failures	0
Subjects enrolled	21
Subjects receiving at least 1 dose of study medication	21 (100.0)
Subjects completing study	18 (85.7)
Subjects who prematurely withdrew from study[a]	3 (14.3)
Adverse event	1 (4.8)
Liver transplant	2 (9.5)

Percentages were based on the number of subjects who received at least 1 dose of study medication.
AE = adverse event; N = number of subjects; n = number of subjects in the specified category.
a. Reasons for withdrawal: 1 subject discontinued before Week 6 due to the AE of transient ischemic attack and 2 subjects discontinued the study to undergo organ transplant.

A summary of baseline demographics is presented for the ITT population in Table 3.

Table 3. Subject Demographics – ITT Population

Demographic	Tafamidis 20 mg (N=21)
Age (year)	
Mean (SD)	63.1 (9.86)
Median	64.3
Range	43.9, 76.8
25th Percentile	56.9
75th Percentile	70.8
Age group, n (%)	
≤ 65 years	11 (52.4)
> 65 years	10 (47.6)
Gender, n (%)	
Male	13 (61.9)
Female	8 (38.1)
Race, n (%)	
Afro-Caribbean	1 (4.8)
Asian	1 (4.8)
Caucasian	19 (90.5)

ITT = intent-to-treat; N = number of subjects; n = number of subjects with specified data; SD = standard deviation.

A summary of baseline characteristics for the ITT population is presented in Table 4.

Table 4. Baseline Characteristics – ITT Population

Characteristic	Tafamidis 20 mg (N=21)
Height (cm)	
Mean (SD)	170.7 (9.43)
Median	172.0
Range	154.0, 189.5
Weight (kg)	
Mean (SD)	72.6 (16.51)
Median	75.0
Range	46.2, 107.7
Screening mBMI[a]	
Mean (SD)	1052.5 (206.66)
Median	1047.8
Range	725.0, 1409.6
Baseline TTR (mg/dL)[b]	
Mean (SD)	19.3 (4.65)
Median	19.8
Range	10.8, 27.4
Karnofsky Performance Status Scale	
Mean (SD)	74.8 (14.01)
Median	70.0
Range	50.0, 90.0
Duration of ATTR-related symptoms (months)	
Mean (SD)	64.7 (60.77)
Median	45.5
Range	5.2, 253.1
Age at ATTR symptom onset (years)	
Mean (SD)	59.3 (9.15)
Median	61.0
Range	43.0, 72.0
Age at ATTR diagnosis (years)	
Mean (SD)	61.6 (9.63)
Median	61.0
Range	43.0, 75.0
NIS Total Score	
Mean (SD)	48.7 (44.31)
Median	45.0
Range	0.0, 131.9
NIS-LL	
Mean (SD)	27.6 (24.67)
Median	18.0
Range	0.0, 69.9

Table 4. Baseline Characteristics – ITT Population

Characteristic	Tafamidis 20 mg (N=21)
Norfolk QOL-DN (TQOL)	
Mean (SD)	47.8 (35.14)
Median	38.0
Range	5.0, 104.0

ATTR = transthyretin amyloidosis; ITT = intent-to-treat; mBMI = modified body mass index; N = number of subjects; n = number of subjects with specified data; NIS = Neuropathy Impairment Score; NIS-LL = Neuropathy Impairment Score–Lower Limb; QOL–DN = quality of life-diabetic neuropathy; SD = standard deviation; TQOL = total quality of life; TTR = transthyretin.

a. mBMI; calculation: (kg/length in m^2) x serum albumin level (g/L). One subject had no mBMI value because there was no screening serum albumin value.

b. One subject had a missing TTR value at Day 0.

Pharmacodynamic Results:

Primary Pharmacodynamic Analysis: Table 5 summarizes TTR stabilization at Week 6 for the ITT population. The determination of TTR stabilization at Week 6 was not possible in 2 subjects: 1 subject discontinued prior to 6 weeks, and 1 subject had a missing baseline value. Consequently, TTR stabilization at Week 6 could only be evaluated for 19 subjects. Samples were deemed stabilized if the difference from Baseline was >32%. In total, 18 of 19 (95%) subjects had stabilized TTR at Week 6.

Table 5. Transthyretin Stabilization at Week 6 – ITT Population

Parameter	Tafamidis 20 mg (N=21)
Week 6 transthyretin stabilization[a]	n=19
Number (%) stabilized	18 (94.7%)
95% confidence interval	74.0%, 99.9%

Percent calculated based on number of subjects providing both Baseline and Week 6 data.
ITT = intent-to-treat; N = number of subjects; n = number of subjects with specified data; TTR = transthyretin.

a. All subjects enrolled who received study medication and had both the baseline and post baseline TTR stabilization measurements.

Secondary Pharmacodynamic Analysis: Table 6 summarizes TTR stabilization at Months 6 and 12 for the ITT population. TTR stabilization (as defined by the TTR stabilization assay) was observed in all subjects (100.0%) who had data at Baseline and at both the Months 6 and 12 Visits. These data demonstrated the persistence of TTR stabilization with chronic dosing of tafamidis.

Table 6. TTR Stabilization at Months 6 and 12 – ITT Population

Parameter	Tafamidis 20 mg (N=21)
Month 6 TTR Stabilization[a]	n=18
Number (%) stabilized[b]	18 (100.0%)
95% confidence interval	81.5%, 100.0%
Month 12 TTR Stabilization[a]	n=17
Number (%) stabilized	17 (100.0%)
95% confidence interval	80.5%, 100.0%

ITT = intent-to-treat; N = number of subjects; n = number of subjects with specified data; TTR = transthyretin.

a. All subjects enrolled who received study medication and had both a baseline and a post-baseline TTR stabilization measurement at these timepoints were included.

b. One subject was not stabilized at Week 6 but was stabilized at Months 3 and 6. He was reflected stabilized at Month 6.

Safety Results: A summary of the most common TEAEs (>5% overall), presented in descending order of incidence for the overall group, regardless of relationship to study medication, is presented in Table 7. The most commonly reported TEAEs overall were fall, diarrhea, pain in extremity, dizziness, dyspnea, vomiting, and constipation.

Table 7. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term Reported in >5% of Subjects in Either Treatment Group

System Organ Class Preferred Term	Number of Subjects (%)	
	Part 1[a] N=21	Overall[b] N=21
Number of subjects with at least 1 non-serious AE	9 (42.9%)	13 (61.9%)
Gastrointestinal disorders	3 (14.3%)	7 (33.3%)
Diarrhoea	2 (9.5%)	5 (23.8%)
Vomiting	2 (9.5%)	3 (14.3%)
Constipation	0 (0.0%)	3 (14.3%)
Nausea	0 (0.0%)	2 (9.5%)
General disorders and administration site conditions	2 (9.5%)	4 (19.0%)
Fatigue	2 (9.5%)	2 (9.5%)
Oedema peripheral	0 (0.0%)	2 (9.5%)
Infections and infestations	0 (0.0%)	4 (19.0%)
Laryngitis	0 (0.0%)	2 (9.5%)
Sinusitis	0 (0.0%)	2 (9.5%)
Injury, poisoning and procedural complications	3 (14.3%)	4 (19.0%)
Fall	3 (14.3%)	4 (19.0%)
Musculoskeletal and connective tissue disorders	3 (14.3%)	6 (28.6%)
Pain in extremity	3 (14.3%)	4 (19.0%)
Muscle spasms	0 (0.0%)	2 (9.5%)
Nervous system disorders	4 (19.0%)	6 (28.6%)
Neuralgia	2 (9.5%)	2 (9.5%)
Paraesthesia	2 (9.5%)	2 (9.5%)
Balance disorder	0 (0.0%)	2 (9.5%)
Dizziness	0 (0.0%)	3 (14.3%)
Syncope	0 (0.0%)	2 (9.5%)
Respiratory, thoracic and mediastinal disorders	2 (9.5%)	5 (23.8%)
Epistaxis	2 (9.5%)	2 (9.5%)
Dyspnoea	0 (0.0%)	3 (14.3%)
Vascular disorders	0 (0.0%)	3 (14.3%)
Hypotension	0 (0.0%)	2 (9.5%)
Orthostatic hypotension	0 (0.0%)	2 (9.5%)

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 or preferred term when counting subjects. If more than 1 event was reported within the system organ class or preferred term, the most severe event with the earliest start date was counted.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
a. All events that started inclusively in the period after the start of study treatment and through Week 6.
b. All events.

Treatment-Related Adverse Events: Table 8 is a summary of AEs judged by the Investigator to be at least possibly related to study medication, presented in descending order of incidence. The most commonly reported treatment-related TEAEs were diarrhea, vomiting, neuralgia, and paresthesia.

Table 8. Summary of Study Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – ITT Population

System Organ Class Preferred Term	Part 1[a] N=21	Overall[b] N=21
Number of subjects with at least 1 non-serious AE	7 (33.3%)	8 (38.1%)
Blood and lymphatic system disorders	0 (0.0%)	1 (4.8%)
Polycythaemia	0 (0.0%)	1 (4.8%)
Cardiac disorders	0 (0.0%)	1 (4.8%)
Ventricular tachycardia	0 (0.0%)	1 (4.8%)
Eye disorders	0 (0.0%)	1 (4.8%)
Dry eye	0 (0.0%)	1 (4.8%)
Gastrointestinal disorders	4 (19.0%)	4 (19.0%)
Diarrhoea	2 (9.5%)	2 (9.5%)
Vomiting	2 (9.5%)	2 (9.5%)
Constipation	0 (0.0%)	1 (4.8%)
Dyspepsia	1 (4.8%)	1 (4.8%)
Nausea	1 (4.8%)	1 (4.8%)
General disorders and administration site conditions	1 (4.8%)	1 (4.8%)
Asthenia	1 (4.8%)	1 (4.8%)
Malaise	1 (4.8%)	1 (4.8%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (4.8%)
Ankle fracture	0 (0.0%)	1 (4.8%)
Musculoskeletal and connective tissue disorders	2 (9.5%)	2 (9.5%)
Arthralgia	1 (4.8%)	1 (4.8%)
Pain in extremity	1 (4.8%)	1 (4.8%)
Nervous system disorders	6 (28.6%)	6 (28.6%)
Neuralgia	2 (9.5%)	2 (9.5%)
Paraesthesia	2 (9.5%)	2 (9.5%)
Balance disorder	0 (0.0%)	1 (4.8%)
Dizziness	0 (0.0%)	1 (4.8%)
Headache	1 (4.8%)	1 (4.8%)
Syncope	1 (4.8%)	1 (4.8%)
Transient ischaemic attack	1 (4.8%)	1 (4.8%)
Renal and urinary disorders	0 (0.0%)	1 (4.8%)
Urinary retention	0 (0.0%)	1 (4.8%)
Vascular disorders	2 (9.5%)	2 (9.5%)
Hypotension	1 (4.8%)	1 (4.8%)
Orthostatic hypotension	1 (4.8%)	1 (4.8%)

Relationships includes possible, probable, definite, or missing relationships. 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 or preferred term when counting subjects. If more than 1 event was reported within the system organ class or preferred term, when counting subjects.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
a. All events that started inclusively in the period after the start of study treatment and through Week 6.
b. All events.

Three subjects experienced Grade 3 AEs. No subjects experienced a TEAE considered life-threatening. The severe TEAEs included dizziness, balance disorder, arthritis and diarrhea (1 subject); subileus syndrome (1 subject) and AV block (1 subject). Of these, dizziness and balance disorder were considered possibly related to study drug.

Serious Adverse Events (SAEs): Table 9 presents a summary of treatment-emergent SAEs. Overall, 8 (38.1%) subjects experienced a total of 13 treatment-emergent SAEs. Of these

SAEs, 9 were considered by the Investigator to be unrelated to study medication and 4 were considered possibly related.

Table 9. Treatment-Emergent Serious Adverse Events – Safety Population

Subject Number	MedDRA Preferred Term	Relationship to Study Medication	Outcome
1	Ankle fracture	Possible	Recovered
-	Arthritis	Unrelated	Recovered
2	Malaise	Possible	Recovered
-	Fall	Unrelated	Recovered
-	Urinary retention	Possible	Recovered
-	Fecaloma	Unrelated	Recovered
3	Subileus	Unrelated	Recovered
4	Carpal tunnel decompression	Unrelated	Recovered
5	Coronary artery stenosis	Unrelated	Recovered
6[a]	Transient ischemic attack	Possible	Recovered
7	Atrioventricular block	Unrelated	Recovered
8	Fall	Unrelated	Recovered
-	Avulsion fracture	Unrelated	Recovered

All AEs were coded using MedDRA dictionary version 10.0.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities.
a. Subject withdrew from the study as a result of this adverse event.

Discontinuations due to AEs: Only one subject discontinued due to an AE. Two subjects discontinued the study to undergo liver transplant. Neither of these subjects reported any AEs following the transplant.

Deaths: There were no deaths reported during the study.

Laboratory Evaluations: There were no clinically relevant mean changes in clinical laboratory parameters over time. Tafamidis had no effect on thyroid function, as indicated by small mean changes from Baseline to Months 6 and 12 for thyroid stimulating hormone, total thyroxine (T4) and free T4. There were no clinically relevant changes in vital signs, or the proportion of subjects with orthostatic hypotension on treatment, or in physical examination findings. Table 10 provides a summary of the incidence of echocardiography pre-specified categorical abnormalities occurring at Baseline and at any time point on-treatment.

All subjects had at least 1 echocardiographic abnormality at Baseline. The most commonly reported echocardiographic abnormalities at Baseline were left ventricular posterior wall thickness and left ventricular septal thickness (≥13 mm), which were reported for 17 of 19 (89.5%) subjects each, and valve thickening reported for 16 of 19 (84.2%) subjects. Review of various echocardiographic qualitative and quantitative measurements including 2-dimensional, flow and tissue Doppler and wall motion did not indicate potential adverse treatment effects, and the observed abnormalities appear consistent with underlying cardiac involvement.

Table 10. Summary of Baseline (Day 0) and Treatment-Emergent (New-Onset) Echocardiography Categorical Abnormalities – Safety Population

Assessment Criterion	Tafamidis 20 mg N=21 N/n (%)[a]	
	Baseline	On-Treatment
Any echocardiogram abnormalities, n (%)	21/21 (100.0)	12/19 (63.2)
Left ventricular septal thickness ≥13 mm	17/19 (89.5)	1/3 (33.3)
LV posterior wall thickness ≥13 mm	17/19 (89.5)	2/3 (66.7)
Right ventricular thickness ≥7 mm	4/17 (23.5)	6/13 (46.2)
Ejection fraction <50%	3/21 (14.3)	2/17 (11.8)
E/E prime septal >15	8/14 (57.1)	2/10 (20.0)
E/E prime lateral >15	5/16 (31.3)	3/15 (20.0)
IVRT ≤70 ms	1/10 (10.0)	2/13 (15.4)
E/A ratio ≥2	3/18 (16.7)	3/16 (18.8)
E deceleration time ≤150 ms	7/18 (38.9)	1/14 (7.1)
Pericardial effusion	1/21 (4.8)	2/19 (10.5)
Valvular abnormalities - thickening	16/19 (84.2)	3/5 (60.0)
Valvular abnormalities - regurgitation	9/19 (47.4)	2/9 (22.2)
Inferior vena cava respiratory variation	5/18 (27.8)	0/13 (0.0)
Abnormal regional wall motion	0/5 (0.0)	2/11 (18.2)

The numerator and denominator for any on-treatment incidence include only subjects with Day 0 values that were not abnormal (i.e., treatment-emergent abnormalities). Abnormalities occurring at Early Termination Visits were not included in the determination of overall abnormalities.
E = early diastolic transmitral flow velocity; E/A = ratio of peak mitral early diastolic and atrial contraction velocity; E/E = early diastolic transmitral flow velocity to the mitral annular velocity; IVRT = isovolumic relaxation time; LV = left ventricular; N = number of subjects; n = number of subjects in specified category.
a. Number with abnormality/Number eligible for assessment (%) at visit.

Table 11 summarizes the incidence of treatment-emergent centrally over-read ECG abnormalities occurring at any time point in the study by assessment and treatment. ECG abnormalities at Baseline were common (16 of 21 [76.2%] subjects), with conduction abnormalities the most frequently reported (13 of 21 [61.9%] subjects), including left anterior hemiblock and first degree atrioventricular block. The most frequently reported treatment emergent abnormality was arrhythmia (8 of 18 [44.4%]) subjects), including premature atrial contractions. Analysis of heart rate and ECG interval measurements showed no clinically relevant effect of tafamidis on cardiac conduction or repolarization.

Table 11. Summary of Central Over-Read Electrocardiogram Abnormalities by Assessment – Safety Population

Criterion	Visit	Tafamidis 20 mg N=21 n (%)
ECG Abnormalities		
Any ECG abnormalities	Pretreatment	16/21 (76.2)
	On-Treatment	9/21 (42.9)
Arrhythmia	Pretreatment	3/21 (14.3)
	On-Treatment	8/18 (44.4)
Rhythm	Pretreatment	3/21 (14.3)
	On-Treatment	1/18 (5.6)
Conduction	Pretreatment	13/21 (61.9)
	On-Treatment	2/8 (25.0)
Morphology	Pretreatment	1/21 (4.8)
	On-Treatment	0/20 (0.0)
Myocardial infarction	Pretreatment	3/21 (14.3)
	On-Treatment	0/18 (0.0)
ST segment	Pretreatment	1/21 (4.8)
	On-Treatment	1/20 (5.0)
T waves	Pretreatment	3/21 (14.3)
	On-Treatment	1/18 (5.6)
Abnormal U waves	Pretreatment	0/21 (0.0)
	On-Treatment	0/21 (0.0)
QT_{c-F} and QT_{c-B} Abnormalities		**n/n[a] (%)**
QT_{c-F} >450 ms	Pretreatment	8/21 (38.1)
	On-Treatment	1/13 (7.7)
QT_{c-F} >500 ms	Pretreatment	1/21 (4.8)
	On-Treatment	0/20 (0.0)
Change in QT_{c-F} between 30 (inclusive) and 60 ms	On-Treatment	4/21 (19.0)
Change in QT_{c-F} ≥60 ms	On-Treatment	0/21 (0.0)
QT_{c-B} >450 ms	Pretreatment	14/21 (66.7)
	On-Treatment	0/7 (0.0)
QT_{c-B} >500 ms	Pretreatment	2/21 (9.5)
	On-Treatment	1/19 (5.3)
Change in QT_{c-B} between 30 (inclusive) and 60 ms	On-Treatment	5/21 (23.8)
Change in QT_{c-B} ≥60 ms	On-Treatment	0/21 (0.0)

QT_{c-B} was based on Bazett's correction; QT_{c-F} was based on Fridericia's correction.
Pretreatment indicates that the subject had at least 1 pretreatment abnormality (at Screen 1 [Days -30 to -1] Baseline [Day 0]). The numerator and denominator for any post first dose incidence included only subjects with pretreatment values that were not abnormal (ie, treatment-emergent abnormalities). On-treatment indicates that the subject had at least 1 post baseline treatment-emergent abnormality for the given parameter during the study. Abnormalities occurring at Early Termination Visits were not included in the determination of overall abnormalities.
ECG = electrocardiogram; N = number of subjects; n = number of subjects in the specified category; QT_{c-B} = rate-corrected QT using Bazett's formula; QT_{c-F} = rate-corrected QT using Fridericia's formula; ST segment = time between the end of ventricular depolarization to the onset of the T wave.
a. Number with abnormality/Number eligible for assessment (%) at visit.

A summary of the incidence of Holter monitoring abnormalities by parameter and overall is provided in Table 12.

Two thirds of the subjects had at least 1 Holter monitoring abnormality at Baseline. The

most common baseline Holter abnormality was atrial tachycardia (11/21, 52.4%). Nine (47.4%) subjects reported a new, treatment-emergent abnormality; the most common was atrial tachycardia (4/9, 44.4%). The pattern of treatment-emergent abnormalities was similar to the baseline findings. This was not unexpected given the age, high prevalence of ectopy at Baseline, and the intermittent nature of these abnormalities.

Table 12. Summary of Holter Monitoring Overall Abnormalities by Parameter – Safety Population

Criterion	Visit	Tafamidis 20 mg N=21 n (%)[a]
Any Holter monitoring abnormalities	Baseline	14/21 (66.7)
	On-Treatment	9/19 (47.4)
Non-sustained ventricular tachycardia (<30 beats)	Baseline	8/21 (38.1)
	On-Treatment	4/11 (36.4)
Atrial fibrillation/flutter	Baseline	1/21 (4.8)
	On-Treatment	1/18 (5.6)
Atrial tachycardia	Baseline	11/21 (52.4)
	On-Treatment	4/9 (44.4)
Sinus pause	Baseline	1/21 (4.8)
	On-Treatment	1/18 (5.6)

The numerator and denominator for any post-dose incidence include only subjects with Day 0 values that were not abnormal (ie, treatment-emergent abnormalities). On-treatment indicates that the subject had at least 1 post baseline treatment-emergent abnormality for the given parameter during the study. Abnormalities occurring at Early Termination Visits were not included in the determination of overall abnormalities.
N = number of subjects; n = number of subjects in the specified category.
a. Number with abnormality/number eligible for assessment (%) at visit.

CONCLUSIONS:

- The results from this open-label study of non-V30M transthyretin amyloidosis with polyneuropathy (ATTR-PN) subjects, which represented an older, more severely affected subject population, strongly supported the observed efficacy of tafamidis in V30M subjects. As in a previous double-blind, placebo-controlled study (safety and efficacy of orally administered Fx-1006A in patients with familial amyloid polyneuropathy (FAP): a randomized, double-blind, placebo-controlled study [NCT00409175]), the consistency of response across endpoints measuring different aspects of this multi-faceted disease was again observed following 12 months treatment with tafamidis. The results indicated the disease modifying utility of tafamidis in treating all subjects with ATTR-PN, regardless of mutation.

- Treatment with tafamidis for 12 months in these older subjects with non-V30M ATTR and significant neurologic and cardiac involvement did not indicate any adverse treatment effect on clinical laboratories, vital signs, echocardiography, ECG, Holter monitor results, or physical examination parameters. Overall, these results demonstrated that an oral daily dose of 20-mg tafamidis was well tolerated in subjects with non-V30M transthyretin amyloidosis.