PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: B3461010

PROTOCOL TITLE: The Effect on Transthyretin Stabilization, Safety, Tolerability, Efficacy and Pharmacokinetics of Orally Administered Tafamidis in Transthyretin Amyloid Polyneuropathy Patients With V30M or Non-V30M Transthyretin: a Phase III, Open-Label Study

Study Center(s): 2 centers in Japan

Study Initiation and Final Completion Dates: 28 November 2011 to 26 February 2014

Phase of Development: Phase 3

Study Objective(s): The objective of this study was to determine transthyretin (TTR) stabilization as well as tafamidis safety and tolerability, efficacy and pharmacokinetics in patients with V30M[Note a] and non-V30M transthyretin familial amyloid polyneuropathy (TTR-FAP).

Primary Objective

To determine TTR stabilization at steady-state, as measured in patients with V30M and non-V30M TTR-FAP.

Secondary Objectives

- To evaluate the safety, tolerability and efficacy of tafamidis in patients with V30M and non-V30M TTR-FAP.
- To characterize tafamidis pharmacokinetics using a population pharmacokinetic approach in patients with V30M and non-V30M TTR-FAP.

Note a: The most common variant associated with polyneuropathy is V30M (valine replaced by methionine at position 30).

METHODS

Study Design: This was a single-arm, open-label, multicenter study designed to determine TTR stabilization as well as tafamidis safety and tolerability, efficacy and population pharmacokinetics in patients with V30M and non-V30M TTR-FAP.

The duration was to continue to be until available from market (up to 3 years). Clinical visits for assessment of TTR stabilization, safety, tolerability, efficacy and tafamidis concentration were scheduled at screening (Days −30 and −1), baseline (Day 0) and at Week 2, Week 4, Week 8, Week 12, Week 26, Week 39, Week 52, Week 78 and then 26-week interval visit and the end of study. The study flowchart is presented in Table 1.

Table 1. Study Flowchart

	Screening	Baseline	Treatment phase									
		Day 0	2 Wk	4 Wk	8 Wk	12 Wk	26 Wk	39 Wk	52 Wk	78 Wk	26 Wk interval	End of study
Allowable window	**Day -30 to Day -1**		**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**
Informed consent	X											
Medical history/demographics	X											
Review of entrance criteria	X	X										
Registration	X	X										
Biopsy to confirm amyloid [a]	X											
Confirmation of V30M or non-V30M genotype	X											
QST for vibration perception in the feet utilizing CASE IV	X											
Physical examination	X						X		X	X		X
Abbreviated physical examination			X	X	X	X		X			X	
Body height	X											
Body weight	X	X			X		X		X	X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for TTR stabilization assay		X			X [b]		X [b]		X [b]	X [b]		X [k]
Blood sample for pharmacokinetic analysis			X [c]	X [c]	X [c]		X [d]		X [b]	X [b]		X [k]
Laboratory tests (hematology, coagulation panel, serum chemistry, and urinalysis)	X	X		X	X	X	X	X	X	X	X	X
Serology (HbsAg, anti-HCV, HIV)	X											
Serum pregnancy test (females of child-bearing potential only)	X			X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of child-bearing potential only)		X										
Serum follicle-stimulating hormone [e]	X											
12-Lead ECG	X	X		X	X	X	X	X	X	X	X	X
Echocardiography		X [f]							X		X [g]	X
NIS [h]		X [f]					X		X	X		X [i]
QST (CASE IV), HRDB, NCS		X [f]					X		X	X		X [i]
Norfolk QOL-DN		X [f]					X		X	X		X [i]
Ambulatory status		X [f]					X		X	X		X [i]
Concomitant medications [j]	X	X	X	X	X	X	X	X	X	X	X	X
Study medication compliance [j]			X	X	X	X	X	X	X	X	X	X
AEs [j]		←										→

Table 1. Study Flowchart

Wk = week; QST = quantitative sensory testing; CASE IV = Computer Aided Sensory Evaluator, Version 4; TTR = transthyretin; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ECG = electrocardiogram; NIS = Neuropathy Impairment Score; HRDB = heart rate response to deep breathing; NCS = nerve conduction studies; Norfolk QOL-DN = Norfolk QOL-Diabetic Neuropathy; AE = adverse event

a. Biopsy had to be performed within 5 years of enrollment. If greater than 5 years, biopsy was repeated at the investigative site.
b. Sampling 3 hours after dosing tafamidis
c. 2 sampling point for each visit; first sample was as soon as when subject arrived at the site prior to tafamidis administration and the second sampling time was at 3 hour after administration of tafamidis.
d. Sampling prior to administration of tafamidis, 3 hours after, 4 hours after, 6 hours after and 10 hours after administration of tafamidis
e. Performed only at 45-60 year old females who had been amenorrhea for at least 2 years.
f. Baseline evaluations could have been performed during the screening period only in cases where scheduling did not permit the examinations at baseline.
g. Performed every 52 weeks after Week 52.
h. NIS testing was performed 2 times at least 24 hours apart within a 1-week period by the same neurologist before and/or at the baseline visit. Both evaluations were completed prior to study medication administration at baseline visit.
i. For study completion or withdrawal after Week 26, these tests were not needed if last test was performed within 12 weeks of study completion or withdrawal or if study completion or withdrawal occurred after Week 78.
j. After Week 12, every 6 weeks telephone contact (did not exceed 7 weeks since last confirmation) was conducted to monitor for AEs, study medication compliance and concomitant medications. Reporting period of serious AE (SAE) was from obtaining the informed consent to 28 calendar days after the last administration. Should an investigator be made aware of any SAE occurring any time after the active reporting period, it was required to be promptly reported.
k. Not performed for study completion or withdrawal after Week 78.

Number of Subjects (Planned and Analyzed): 10 subjects (planned and analyzed)

Diagnosis and Main Criteria for Inclusion: Subjects were male and female aged ≥20 through 75 years who had amyloid documented by biopsy and V30M or a TTR mutation associated with peripheral neuropathy. Subjects had peripheral and/or autonomic neuropathy with a Karnofsky Performance Status ≥50.

Study Treatment: All enrolled subjects were to receive oral tafamidis 20 mg soft gelatin capsules once daily until available from market (up to 3 years). Study medication was to be taken at the same time each day throughout the treatment period.

Efficacy Endpoints: The primary endpoint was TTR stabilization at Week 8 compared with baseline, as measured by a validated immunoturbidimetric assay.

The secondary endpoints included the following:

- Change from baseline on the following scales:
    - Neuropathy Impairment Score (NIS) (total), Neuropathy Impairment Score-Lower Limb (NIS-LL) and Neuropathy Impairment Score-Upper Limb (NIS-UL) Score
    - Total quality of life (TQOL) score and five domains as measured by the Norfolk QOL-Diabetic Neuropathy (Norfolk QOL-DN)
    - Summated 7 Nerve Tests Normal Deviate Score (Σ7 NTs NDS) as measured by nerve conduction studies (NCS), vibration detection threshold (VDT) and heart rate response to deep breathing (HRDB)
    - Summated 3 Nerve Tests Small Fiber Normal Deviate Score (Σ3 NTSF NDS) as measured by cooling and heat pain thresholds utilizing Computer Aided Sensory Evaluator, Version 4 (CASE IV) and HRDB
    - Modified body mass index (mBMI), calculated by multiplying the body mass index (BMI) (kg/m^2) by serum albumin level (g/L)
    - Ambulatory status (according to walking ability scale in polyneuropathy disability score)
- TTR stabilization at each follow-up visit after Week 8

Pharmacokinetic Evaluations: Blood samples for determination of plasma levels of tafamidis were collected at Week 2, Week 4, Week 8, Week 26, Week 52, Week 78 and study completion or withdrawal before Week 78. Each 5 mL whole blood sample was collected into potassium edetic acid tubes. At least 1.5 mL plasma was collected from each sample. Plasma was stored in polypropylene tubes at –70ºC until shipment to the analytical lab.

Safety Evaluations: Safety assessments to be performed during the study included physical examinations; measurement of vital signs; clinical laboratory evaluations, including hematology, coagulation panel, and serum chemistry, electrocardiogram (ECG), echocardiography and monitoring of adverse events (AEs).

Statistical Methods:

Efficacy

The full analysis set (FAS) included all subjects who received at least one dose of tafamidis. All efficacy analyses were performed on the FAS.

The pharmacodynamic analysis set included all subjects treated who had at least 1 of TTR stabilization assessment in treatment period. The TTR stabilization analyses were performed on the pharmacodynamic analysis set.

Efficacy analyses were performed in a descriptive manner. The number and percentage of responders and its 95% confidence interval (CI) were calculated for TTR stabilization (ie, the percent stabilization was equal to or more than 32%) and for NIS-LL (ie, an increase from baseline in the NIS-LL <2).

Pharmacokinetics

The pharmacokinetic analysis set included all subjects randomized and treated who had at least 1 quantifiable plasma tafamidis concentration.

The pharmacokinetic parameters for tafamidis were obtained using population pharmacokinetic approach. The analysis plan was prepared separately as population pharmacokinetic modeling analysis plan.

Safety

The safety analysis set included all subjects who received at least one dose of tafamidis soft gelatin capsule 20 mg.

Safety analyses were performed in a descriptive manner in accordance with Pfizer Data Standards (PDS).

RESULTS

Subject Disposition and Demography: A total of 10 subjects were enrolled (assigned to treatment) in the study. Of these subjects, 7 completed study treatment and 3 discontinued from the study. All subjects were analyzed for pharmacokinetics, pharmacodynamics, efficacy, and safety (Table 2).

Table 2. Subject Disposition and Data Sets Analyzed

Number of Subjects	Tafamidis 20 mg
Assigned to study treatment	10
Treated	10
Completed	7
Discontinued	3
Death	2
Other (unable to visit the site due to disease progression)	1
Data Sets Analyzed	10
Pharmacokinetic analysis set	10
Pharmacodynamic analysis set	10
Full analysis set	10
Safety analysis set	10

Demographic and baseline characteristics are presented in Table 3.

Table 3. Demographic and Baseline Characteristics

Number of Subjects	Tafamidis 20 mg N=10
Sex	
Male	7
Female	3
Age (years)	
<20	0
20-44	1
45-64	5
≥65	4
Mean (SD)	60.1 (13.0)
Range	35-73
Weight (kg)	
Mean (SD)	55.6 (10.8)
Range	42.2-73.3
BMI (kg/m^2)	
Mean (SD)	20.9 (3.1)
Range	18.2-26.3
Height (cm)	
Mean (SD)	162.5 (6.3)
Range	152.4-170.0
TTR genotype, n (%)	
S77Y	1 (10.0)
V30M	9 (90.0)

BMI = Body mass index; SD = standard deviation

Efficacy Results: The percentage of subjects achieving TTR stabilization is summarized in Table 4. All subjects achieved TTR stabilization (the percent stabilization was equal to or more than 32%) at Week 8 and Week 26, and 9 of 10 subjects (90.0%) at Week 52 and 8 of 10 subjects (80.0%) at Week 78 achieved TTR stabilization.

Table 4. TTR Stabilization Status

	Tafamidis 20 mg N=10
Week 8	
Stabilized[a]/number of evaluable subjects	10/10
Percent stabilized (95% CI)	100.0% (69.2, 100.0)
Week 26	
Stabilized[a]/number of evaluable subjects	10/10
Percent stabilized (95% CI)	100.0% (69.2, 100.0)
Week 52	
Stabilized[a]/number of evaluable subjects	9/10
Percent stabilized (95% CI)	90.0% (55.5, 99.7)
Week 78	
Stabilized[a]/number of evaluable subjects	8/10
Percent stabilized (95% CI)	80.0% (44.4, 97.5)

CI = confidence interval; TTR = transthyretin
Missing data in TTR stabilization were dealt as non-TTR stabilization. Two subjects had missing data at Week 78 (Table 5).
a. The percent stabilization is equal to or more than 32%.

Changes from baseline in NIS, NIS-LL, and NIS-UL scores are summarized in Table 5. Higher scores on each item of NIS indicate worse impairment. Thus, increases from baseline reflect a worsening in impairment.

Table 5. Change From Baseline in NIS, NIS-LL, and NIS-UL Scores

Number	Sex	Age	Geno-type	NIS Total				NIS-LL				NIS-UL			
				BL	Change from BL			BL	Change from BL			BL	Change from BL		
					W 26	W 52	W 78		W 26	W 52	W 78		W 26	W 52	W 78
1	M	73	V30M	1.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	1.0	0.0	0.0	−1.0
2	F	46	V30M	18.0	−0.6	0.5	ND	14.8	0.7	0.8	ND	3.3	−1.3	−0.3	ND
3	F	35	V30M	3.5	0.0	−1.0	−0.3	3.5	−1.3	−1.0	−0.3	0.0	1.3	0.0	0.0
4	M	48	V30M	15.8	1.8	0.0	2.5	11.3	0.8	1.8	1.8	4.5	1.0	−1.8	0.8
5	F	69	V30M	50.9	0.3	13.3	22.6	30.3	−1.1	1.7	3.2	20.6	1.4	11.6	19.4
6	M	63	V30M	0.5	1.5	15.0	7.0	0.5	1.0	6.0	4.0	0.0	0.5	9.0	3.0
7	M	60	S77Y	39.1	29.3	22.5	35.4	19.0	16.3	10.4	14.5	20.1	13.0	12.1	20.9
8	M	71	V30M	63.7	9.3	15.7	ND	28.4	6.4	10.6	ND	35.3	2.9	5.1	ND
9	M	73	V30M	67.0	−3.3	6.0	7.5	36.8	−3.3	−0.3	0.3	30.3	0.0	6.3	7.3
10	M	63	V30M	50.8	5.4	11.0	4.5	25.5	1.1	6.3	2.0	25.3	4.3	4.8	2.5
Mean				31.03	4.37	8.30	9.90	16.99	2.06	3.62	3.30	14.03	2.31	4.68	6.59
(SD)				(26.260)	(9.408)	(8.326)	(12.584)	(13.143)	(5.565)	(4.374)	(4.739)	(13.716)	(4.066)	(5.103)	(8.724)

BL = baseline; NIS = Neuropathy Impairment Score; NIS-LL = Neuropathy Impairment Score-Lower Limb; NIS-UL = Neuropathy Impairment Score-Upper Limb; SD = standard deviation; ND = not done

Two subjects had missing data at Week 78. One subject discontinued due to death on Day 431, and the other subject could not visit the site at Week 78 due to disease progression.

Changes from baseline in TQOL and each domain are summarized in Table 6 and Table 7, respectively. Higher scores on each item of the Norfolk QOL-DN TQOL indicate worse QOL. Thus, increases from baseline reflect a worsening in QOL.

Table 6. Change From Baseline in TQOL by Norfolk QOL-DN

	Tafamidis 20 mg N=10
Baseline, n	10
Mean (SD)	52.9 (32.76)
Median	54.5
Range	4, 105
Change from baseline	
Week 26, n	10
Mean (SD)	11.8 (20.01)
Median	5.5
Range	−6, 54
Week 52, n	10
Mean (SD)	9.1 (12.49)
Median	10.0
Range	−14, 26
Week 78, n	8
Mean (SD)	10.8 (13.69)
Median	12.5
Range	−7, 34

SD = standard deviation; Norfolk QOL-DN = Norfolk QOL-Diabetic Neuropathy; TQOL = total quality of life

Table 7. Change From Baseline in Each Domain by Norfolk QOL-DN

	Tafamidis 20 mg N=10				
	Physical functioning /large fiber	Activities of daily living	Symptoms	Small fiber	Autonomic
Baseline, n	10	10	10	10	10
Mean (SD)	25.6 (15.28)	8.5 (7.63)	8.5 (5.34)	6.3 (5.31)	4.0 (3.06)
Median	24.5	7.5	8.5	5.5	4.0
Range	3, 48	0, 20	0, 18	0, 13	0, 9
Change from baseline					
Week 26, n	10	10	10	10	10
Mean (SD)	4.8 (10.02)	1.2 (3.61)	2.6 (3.47)	1.9 (4.25)	1.3 (1.42)
Median	0.0	0.5	3.0	0.5	1.0
Range	−5, 27	−5, 8	−2, 7	−2, 11	0, 4
Week 52, n	10	10	10	10	10
Mean (SD)	2.2 (8.87)	0.8 (3.52)	4.0 (5.73)	1.6 (2.32)	0.5 (1.43)
Median	3.5	1.0	4.0	0.5	0.0
Range	−12, 16	−7, 5	−3, 16	−1, 6	−1, 3
Week 78, n	8	8	8	8	8
Mean (SD)	4.1 (7.83)	0.6 (2.33)	3.1 (3.94)	2.1 (3.76)	0.8 (1.91)
Median	4.0	0.5	3.0	0.5	0.5
Range	−6, 18	−4, 4	−2, 10	−3, 8	−2, 4

SD = standard deviation; Norfolk QOL-DN = Norfolk QOL-Diabetic Neuropathy

Changes from baseline in Σ7 NTs NDS and Σ3 NTSF NDS are summarized in Table 8. A higher score indicates worse nerve function. Thus, increases from baseline reflect a worsening in nerve function.

Table 8. Change From Baseline in Σ7 NTs NDS and Σ3 NTSF NDS

	Tafamidis 20 mg N=10	
	Σ7 NTs NDS	**Σ3 NTSF NDS**
Baseline, n	10	10
Mean (SD)	8.33 (5.574)	6.39 (3.160)
Median	8.02	5.75
Range	−0.6, 16.6	1.4, 11.2
Change from baseline		
Week 26, n	10	10
Mean (SD)	0.55 (2.657)	0.16 (1.619)
Median	1.10	0.31
Range	−6.3, 3.3	−3.4, 2.2
Week 52, n	10	10
Mean (SD)	1.04 (2.992)	−0.13 (1.334)
Median	1.26	−0.04
Range	−4.8, 5.0	−2.0, 2.6
Week 78, n	8	8
Mean (SD)	1.92 (5.129)	0.40 (1.985)
Median	0.56	−0.33
Range	−3.1, 12.8	−1.6, 4.4

SD = standard deviation; Σ7 NTs NDS = Summated 7 Nerve Tests Normal Deviate Score;
Σ3 NTSF NDS = Summated 3 Nerve Tests Small Fiber Normal Deviate Score

Changes from baseline in mBMI are summarized in Table 9. Decreases from baseline reflect a worsening.

Table 9. Change From Baseline in mBMI

	Tafamidis 20 mg N=10
Baseline, n	10
Mean (SD)	805.70 (193.378)
Median	728.60
Range	577.3, 1095.0
Change from baseline	
Week 8, n	10
Mean (SD)	74.86 (88.706)
Median	79.98
Range	−92.0, 182.7
Week 26, n	10
Mean (SD)	26.61 (61.862)
Median	33.47
Range	−77.1, 148.8
Week 52, n	10
Mean (SD)	64.86 (80.016)
Median	61.80
Range	−82.3, 207.8
End of study, n	7
Mean (SD)	53.65 (81.386)
Median	82.77
Range	−97.5, 150.1

SD = standard deviation; mBMI = modified body mass index

The shift from baseline in ambulatory status is summarized in Table 10. The ambulatory status at Week 26 improved in 1 subject, worsened in 2 subjects, and was unchanged in 7 subjects, at Week 52 improved in 1 subject, worsened in 3 subjects, and was unchanged in 6 subjects, and at Week 78 improved in 1 subject, worsened in 4 subjects, and was unchanged in 3 subjects.

Table 10. Shift From Baseline in Ambulatory Status

Visit	Tafamidis 20 mg (N=10)							
	n	Baseline status	Ambulatory status					
			0	1	2	3a	3b	4
Week 26	10	0						
		1	1	2				
		2			3	1		
		3a				1	1	
		3b					1	
		4						
Week 52	10	0						
		1	1	1	1			
		2			3	1		
		3a				1	1	
		3b					1	
		4						
Week 78	8	0						
		1	1	1		1		
		2			2	1		
		3a					2	
		3b						
		4						

0: Good
1: Sensory disturbances in the feet but able to walk without difficulty
2: Some difficulties with walking but can walk without aid
3a: Able to walk with 1 stick or crutch
3b: Able to walk with 2 sticks or crutches
4: Not ambulatory, confined to a wheelchair or bedridden

Pharmacokinetic and Pharmacodynamic Results: The mean tafamidis concentration at 3 hours after administration of tafamidis 20 mg achieved steady state after Week 8. At Week 8, Week 26, Week 52 and Week 78, the mean tafamidis concentrations were 2773.0, 2739.0, 2829.0 and 3655.0 ng/mL, respectively. The mean percent stabilization of subjects with V30M or non-V30M TTR-FAP at 3 hours after administration of tafamidis 20 mg at Week 8, Week 26, Week 52 and Week 78 were 167.8%, 196.1%, 144.3% and 258.8%, respectively (Table 11). The TTR stabilization of all subjects except 1 subject at Week 52 achieved more than 32%, which was the prior definition of TTR stabilization, at 3 hours after administration at Week 8, Week 26, Week 52. At Week 78, 8 subjects achieved the TTR stabilization, and 2 subjects had missing data. Results of population pharmacokinetic analysis were reported separately in the planned population modeling analysis report.

The relationship between tetramer stabilization and tafamidis: TTR stoichiometry observed in this study is consistent with Study Fx-002.

Table 11. Summary of Tafamidis Concentration and TTR Stabilization

Number	Sex	Age	Genotype	Week 8		Week 26		Week 52		Week 78	
				Tafamidis concentration (ng/mL)	TTR stabilization (%)	Tafamidis concentration (ng/mL)	TTR stabilization (%)	Tafamidis concentration (ng/mL)	TTR stabilization (%)	Tafamidis concentration (ng/mL)	TTR stabilization (%)
1	M	73	V30M	7260	131.5	7690	129.3	8270	141.6	7930	210.9
2	F	46	V30M	1730	44.4	1550	101.6	1660	28.4	ND	ND
3	F	35	V30M	3000	178	1860	89.2	2480	102.7	3430	171.9
4	M	48	V30M	1910	99.8	1980	126.4	1870	81.4	3350	173.9
5	F	69	V30M	1780	196.4	2630	246.3	1330	152.6	1880	245.6
6	M	63	V30M	2450	165.3	1570	129.7	2120	123.6	3010	175.2
7	M	60	S77Y	1790	352.5	2030	401.1	1690	328.4	1550	426.6
8	M	71	V30M	1530	195	2000	247.3	1640	126.9	ND	ND
9	M	73	V30M	2010	166.9	1950	204.5	1430	98	1890	246.2
10	M	63	V30M	4270	148.5	4130	285.5	5800	259.1	6200	419.7
Mean (SD)				2773.0 (1777.71)	167.8 (79.81)	2739.0 (1893.25)	196.1 (99.62)	2829.0 (2315.58)	144.3 (87.65)	3655.0 (2268.08)	258.8 (105.85)

TTR = transthyretin; SD = standard deviation; ND = not done
Two subjects had missing data at Week 78. One subject discontinued due to death on Day 431, and the other subject could not visit the site at Week 78 due to disease progression.

Safety Results: Treatment-emergent AEs are summarized in Table 12.

Table 12. Summary of Treatment-Emergent Adverse Events

Number of Subjects, n (%)	Tafamidis 20 mg	
	All causalities	Treatment related
Subjects evaluable for AEs	10	10
Number of AEs	85	2
Subjects with AEs	10 (100.0)	2 (20.0)
Subjects with SAEs	7 (70.0)	1 (10.0)
Subjects with severe AEs	3 (30.0)	1 (10.0)
Subjects discontinued due to AEs	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	1 (10.0)	0

AE = adverse event; SAE = serious adverse event

Incidence of treatment-emergent non-serious AEs is summarized by causality in Table 13.

The most common AEs (all causalities) (≥2 subjects) were nasopharyngitis and muscular weakness (5 subjects each), thermal burn (3 subjects), and cataract, vitreous opacities, nausea, vomiting, muscle spasms, myalgia, and insomnia (2 subjects each).

Table 13. Incidence of Treatment-Emergent Non-Serious Adverse Events

System Organ Class MedDRA Preferred Term Number of Subjects, n (%)	Tafamidis 20 mg N=10	
	All causalities	Treatment related
Blood and lymphatic system disorders	1 (10.0)	0
Iron deficiency anaemia	1 (10.0)	0
Cardiac disorders	2 (20.0)	0
Atrioventricular block second degree	1 (10.0)	0
Palpitations	1 (10.0)	0
Ear and labyrinth disorders	2 (20.0)	0
Ear discomfort	1 (10.0)	0
Meniere's disease	1 (10.0)	0
Eye disorders	3 (30.0)	0
Cataract	2 (20.0)	0
Conjunctivitis	1 (10.0)	0
Dry eye	1 (10.0)	0
Eye discharge	1 (10.0)	0
Vitreous opacities	2 (20.0)	0
Gastrointestinal disorders	3 (30.0)	1 (10.0)
Diarrhoea	1 (10.0)	0
Gingival swelling	1 (10.0)	1 (10.0)
Nausea	2 (20.0)	0
Paraesthesia oral	1 (10.0)	0
Stomatitis	1 (10.0)	0
Vomiting	2 (20.0)	0
General disorders and administration site conditions	2 (20.0)	0
Oedema	1 (10.0)	0
Pyrexia	1 (10.0)	0
Infections and infestations	7 (70.0)	0
Bronchitis	1 (10.0)	0
Hordeolum	1 (10.0)	0
Influenza	1 (10.0)	0
Nasopharyngitis	5 (50.0)	0
Oral herpes	1 (10.0)	0
Tinea capitis	1 (10.0)	0
Tinea pedis	1 (10.0)	0
Injury, poisoning and procedural complications	4 (40.0)	0
Laceration	1 (10.0)	0
Limb injury	1 (10.0)	0
Muscle strain	1 (10.0)	0
Thermal burn	3 (30.0)	0
Metabolism and nutrition disorders	1 (10.0)	0
Hyperlipidaemia	1 (10.0)	0
Musculoskeletal and connective tissue disorders	9 (90.0)	0
Back pain	1 (10.0)	0
Flank pain	1 (10.0)	0
Muscle spasms	2 (20.0)	0
Muscular weakness	5 (50.0)	0
Myalgia	2 (20.0)	0
Pain in extremity	1 (10.0)	0
Trigger finger	1 (10.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (10.0)	0
Neoplasm skin	1 (10.0)	0

Table 13. Incidence of Treatment-Emergent Non-Serious Adverse Events

System Organ Class MedDRA Preferred Term Number of Subjects, n (%)	Tafamidis 20 mg N=10	
	All causalities	Treatment related
Nervous system disorders	2 (20.0)	0
Ataxia	1 (10.0)	0
Dementia	1 (10.0)	0
Headache	1 (10.0)	0
Hypoaesthesia	1 (10.0)	0
Loss of consciousness	1 (10.0)	0
Psychiatric disorders	3 (30.0)	0
Anxiety	1 (10.0)	0
Insomnia	2 (20.0)	0
Reproductive system and breast disorders	1 (10.0)	0
Gynaecomastia	1 (10.0)	0
Respiratory, thoracic and mediastinal disorders	2 (20.0)	0
Cough	1 (10.0)	0
Rhinitis allergic	1 (10.0)	0
Sleep apnoea syndrome	1 (10.0)	0
Skin and subcutaneous tissue disorders	5 (50.0)	0
Blister	1 (10.0)	0
Decubitus ulcer	1 (10.0)	0
Dermatitis	1 (10.0)	0
Hyperhidrosis	1 (10.0)	0
Rash	1 (10.0)	0
Skin ulcer	1 (10.0)	0
Solar dermatitis	1 (10.0)	0
Urticaria	1 (10.0)	0

MedDRA = Medical Dictionary for Regulatory Activities (version 16.1)

SAEs are summarized in Table 14. A total of 13 SAEs were reported in 7 subjects. Of these 13 events, sudden death was assessed by the investigator as related to the study drug.

Table 14. SAEs

Number	Sex	Age[a]	MedDRA Preferred Term	Severity	Event Onset Day	Event Stop Day	Study Drug Action	Relationship to Treatment	Outcome
1	Female	47	Completed suicide	Severe	431	NA	Dose not changed	Unrelated	Fatal
2	Female	37	Sick sinus syndrome	Moderate	619	686	Dose not changed	Unrelated	Recovered
3	Male	48	Pyelonephritis	Moderate	31	40	Dose not changed	Unrelated	Recovered
		49	Atrioventricular block second degree	Moderate	364	433	Temporarily withdrawn	Unrelated	Recovered
		49	Burns third degree	Moderate	258	288	Dose not changed	Unrelated	Recovered
4	Male	60	Pneumonia bacterial	Moderate	4	20	Dose not changed	Unrelated	Recovered
		61	Ileus [b]	Severe	644	736	Temporarily withdrawn	Unrelated	Recovered
5	Male	72	Decreased appetite	Moderate	390	431	Dose not changed	Unrelated	Recovered
		73	Urinary retention	NA	578	NA	Post-therapy	Unrelated	Not recovered
		73	Benign prostatic hyperplasia	NA	578	NA	Post-therapy	Unrelated	Recovering
6	Male	74	Pneumonia bacterial	Moderate	301	351	Dose not changed	Unrelated	Recovered
		75	Sudden death	Severe	651	NA	NA	Related	Fatal
7	Male	63	Pneumonia bacterial	Moderate	29	57	Dose not changed	Unrelated	Recovered

SAE = serious adverse event, MedDRA = Medical Dictionary for Regulatory Activities (version 16.1)
a. Age at date of serious adverse event onset.
b. This event was coded as 'intestinal obstruction' in the corporate safety database.

Two deaths (completed suicide and sudden death) were reported in this study (Table 14).

A 47-year-old female subject committed suicide after receiving tafamidis meglumine for a total of 430 days. The investigator considered that the subject committed suicide because of disease and that it was not related to the study drug.

A 75-year-old male subject died after receiving tafamidis meglumine for a total of 650 days. The investigator commented that although the subject suddenly went into cardiopulmonary arrest and the possibility of cardiac disease and heavy bleeding were considered, it was difficult to identify the immediate cause of death because autopsy and diagnostic imaging were not performed. Thus, the investigator considered that the causal relationship with tafamidis meglumine could not be ruled out.

No permanent discontinuations or dose reductions due to AEs were reported in this study. One subject temporarily discontinued the treatment due to ileus. This event was severe in severity and confirmed to have resolved.

The laboratory test abnormalities in retinol-binding protein, N-terminal pro-B-type natriuretic peptide, and transthyretin (pre-albumin) were reported in all subjects at baseline and during the study. The incidences of other laboratory test abnormalities were generally infrequent except decreased red blood cell count (50.0%). There was a laboratory test abnormality reported as an AE (iron deficiency anaemia) in 1 subject. There were no vital sign abnormalities reported as AEs during the study. There was an ECG abnormality reported as an AE (atrioventricular block second degree) in 1 subject. This AE was moderate in severity and was not considered by the investigator to be related to the study drug. No significant change of echocardiography compared to baseline was observed until end of study. The most commonly reported abnormalities of physical examination were neurological and musculoskeletal findings that appeared to be related to the underlying TTR-FAP disease.

CONCLUSION(S):

Study B3461010 was a single-arm, open-label, multicenter study designed to determine TTR stabilization as well as tafamidis safety and tolerability, efficacy and population pharmacokinetics in patients with V30M and non-V30M TTR-FAP.

The TTR genotypes were V30M in 9 subjects and non-V30M in 1 subject out of 10 subjects who enrolled this study.

All enrolled patients were to receive oral tafamidis 20 mg soft gelatin capsules once daily until available from market. After marketing approval of tafamidis, the subjects were to receive continued study treatment within the framework of a post-marketing study until the product became available at medical institutions. The median duration of treatment was 713.5 days (range: 380 to 796 days).

Key outcomes included:

- All subjects achieved TTR stabilization (the percent stabilization was equal to or more than 32%) at Week 8 and Week 26. Nine of 10 subjects (90.0%) achieved TTR stabilization at Week 52, and 8 of 10 subjects (80.0%) achieved TTR stabilization at Week 78.

- The percentage (95% CI) of responders in NIS-LL score (the change in NIS-LL score was less than 2) was 80.0% (44.4, 97.5) at Week 26, 60.0% (26.2, 87.8) at Week 52, and 40.0% (12.2, 73.8) at Week 78.

- The treatment with tafamidis 20 mg was generally safe and well-tolerated. Most of AEs were mild or moderate in severity. No permanent discontinuations due to AEs were reported in this study. A total of 13 SAEs were reported in 7 subjects. Of these events, sudden death was assessed by the investigator as related to the study drug. Two deaths (completed suicide and sudden death) were reported in this study.