EU Clinical Trials Register

Clinical trial results:
Open-Label Safety and Efficacy Evaluation of FX-1006A in Subjects With Transthyretin (TTR) Amyloidosis

Summary

EudraCT number	2009-011535-12
Trial protocol	DE SE FR PT IT
Global end of trial date	08 July 2020

Results information

Result version number	v1 (current)
This version publication date	23 July 2021
First version publication date	23 July 2021

Trial information

Trial identification

Sponsor protocol code	B3461023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00925002
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To obtain additional, long-term, open-label safety and efficacy data for tafamidis in subjects with transthyretin (TTR) familial amyloid polyneuropathy (ATTR-PN); To continue to provide the investigational product tafamidis to subjects with ATTR-PN who have completed Protocol Fx-006 (NCT00791492) or Protocol Fx1A-201 (NCT00630864).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 August 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Portugal: 49
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	93
EEA total number of subjects	74

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	76
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects enrolled in B3461023 had ATTR-PN, had not undergone liver/heart transplantation, and completed either B3461021 (Fx-006 [NCT00791492]: extension to Fx-005 [NCT00409175]) or B3461022 (Fx1A-201 [NCT00630864]). Val30Met (V30M): valine replaced by methionine in position 30 of TTR protein; NonVal30Met (NonV30M): TTR mutations other than V30M.

Pre-assignment

Screening details:

Baseline (except treatment-emergent adverse events) was last measurement prior to 1st dose in Fx-005 (V30M) or Fx1A-201 (NonV30M). V30M: data from Baseline to Month 18 from Fx-005; after Month 18 to Month 30 from Fx-006; after Month 30 from B3461023. NonV30M: Baseline to Month 12 from Fx1A-201, after Month 12 from B3461023.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Val30Met: Tafamidis Then Tafamidis

Arm description:

Val30Met subjects who received tafamidis in study Fx-005 (B3461020), continued the same in study Fx-006 (B3461021), received tafamidis 20 milligrams (mg) soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Arm type	Experimental
Investigational medicinal product name	Tafamidis
Investigational medicinal product code	PF-06291826
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Subjects received tafamidis at a dose of 20 mg, orally once daily.

Arm title	Val30Met: Placebo Then Tafamidis

Arm description:

Val30Met subjects who received placebo in study Fx-005 (B3461020) and assigned to receive tafamidis in study Fx-006 (B3461021) and study B3461023 (Fx1A-303), received tafamidis 20 mg soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Arm type	Experimental
Investigational medicinal product name	Tafamidis
Investigational medicinal product code	PF-06291826
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Subjects received tafamidis at a dose of 20 mg, orally once daily.

Arm title	NonVal30Met: Tafamidis

Arm description:

NonVal30Met subjects who received tafamidis in study Fx1A-201 (B3461022), received tafamidis 20 mg soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Arm type	Experimental
Investigational medicinal product name	Tafamidis
Investigational medicinal product code	PF-06291826
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Subjects received tafamidis at a dose of 20 mg, orally once daily.

Number of subjects in period 1	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis	NonVal30Met: Tafamidis
Started	38	37	18
Treated	38	37	18
Completed	32	28	8
Not completed	6	9	10
Adverse event, serious fatal	1	1	5
Subject withdrew consent	1	3	3
Adverse event, non-fatal	3	1	2
Unspecified	1	4	-

Baseline characteristics

Reporting groups

Reporting group title	Val30Met: Tafamidis Then Tafamidis
Reporting group description:	

Val30Met subjects who received tafamidis in study Fx-005 (B3461020), continued the same in study Fx-006 (B3461021), received tafamidis 20 milligrams (mg) soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Reporting group title	Val30Met: Placebo Then Tafamidis
Reporting group description:	

Val30Met subjects who received placebo in study Fx-005 (B3461020) and assigned to receive tafamidis in study Fx-006 (B3461021) and study B3461023 (Fx1A-303), received tafamidis 20 mg soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Reporting group title	NonVal30Met: Tafamidis
Reporting group description:	

NonVal30Met subjects who received tafamidis in study Fx1A-201 (B3461022), received tafamidis 20 mg soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Reporting group values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis	NonVal30Met: Tafamidis
Number of subjects	38	37	18
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	33	34	9
From 65-84 years	5	3	9
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	40.7	38.6	63.6
standard deviation	± 14.03	± 13.76	± 9.15
Sex: Female, Male			
Units: Subjects			
Female	20	21	6
Male	18	16	12
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	33	34	17
Latino American	5	3	0
Afro-Caribbean	0	0	1

Reporting group values	Total		
Number of subjects	93		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	76		
From 65-84 years	17		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	47		
Male	46		
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	84		
Latino American	8		
Afro-Caribbean	1		

End points

End points reporting groups

Reporting group title	Val30Met: Tafamidis Then Tafamidis

Reporting group description:

Val30Met subjects who received tafamidis in study Fx-005 (B3461020), continued the same in study Fx-006 (B3461021), received tafamidis 20 milligrams (mg) soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Reporting group title	Val30Met: Placebo Then Tafamidis

Reporting group description:

Val30Met subjects who received placebo in study Fx-005 (B3461020) and assigned to receive tafamidis in study Fx-006 (B3461021) and study B3461023 (Fx1A-303), received tafamidis 20 mg soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Reporting group title	NonVal30Met: Tafamidis

Reporting group description:

NonVal30Met subjects who received tafamidis in study Fx1A-201 (B3461022), received tafamidis 20 mg soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Primary: Val30Met Group: Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Baseline

End point title	Val30Met Group: Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Baseline[1][2]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. Total possible NIS-LL score range 0-88, high score=more impairment. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure.

End point type	Primary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461020 (Fx-005)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: units on a scale				
arithmetic mean (standard deviation)	6.8 (± 10.8)	11.6 (± 14.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Change From B3461020 Baseline in Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Month 30

End point title	Val30Met Group: Change From B3461020 Baseline in Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Month 30[3][4]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. Total possible NIS-LL score range 0-88, high score=more impairment. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "number of subjects analysed (N)" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461020 (Fx-005), Month 30

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: units on a scale				
least squares mean (standard error)	3.8 (± 1.5)	6.4 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Change From B3461020 Baseline in Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Month 66

End point title	Val30Met Group: Change From B3461020 Baseline in Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Month 66[5][6]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. Total possible NIS-LL score range 0-88, high score=more impairment. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461020 (Fx-005), Month 66

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	31		
Units: units on a scale				
least squares mean (standard error)	7.8 (± 1.6)	11.3 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Baseline

End point title	NonVal30Met Group: Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Baseline[7][8]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. Total possible NIS-LL score range 0-88, high score=more impairment. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure.

End point type	Primary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461022 (Fx1A-201)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the

baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
arithmetic mean (standard deviation)	31.1 (± 24.4)			

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Change From B3461022 Baseline in Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Month 12

End point title	NonVal30Met Group: Change From B3461022 Baseline in Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Month 12[9][10]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. Total possible NIS-LL score range 0-88, high score=more impairment. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure.

End point type	Primary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461022 (Fx1A-201), Month 12

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
least squares mean (standard error)	2.5 (± 2.0)			

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Change From B3461022 Baseline in Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Month 60

End point title	NonVal30Met Group: Change From B3461022 Baseline in Neuropathy Impairment Score Lower Limb (NIS-LL) Score at Month 60[11][12]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. Total possible NIS-LL score range 0-88, high score=more impairment. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461022 (Fx1A-201), Month 60

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: units on a scale				
least squares mean (standard error)	12.0 (± 2.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Baseline

End point title	Val30Met Group: Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Baseline[13][14]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire; assessed impact of DN on health related QOL of subjects with DN. Scoring was based on 35 questions that yield a TQOL as well as 5 subscale scores: symptoms, activities of daily living (ADLs), large fiber neuropathy/physical functioning, small fiber neuropathy, and autonomic neuropathy. TQOL score: sum of all items, total possible score range= -2 to 138, where higher score=worse QOL. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline of B3461020 (Fx-005)

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: units on a scale				
arithmetic mean (standard deviation)	24.1 (± 26.3)	29.9 (± 30.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Change From B3461020 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 30

End point title	Val30Met Group: Change From B3461020 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 30[15][16]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire; assessed impact of DN on health related QOL of subjects with DN. Scoring was based on 35 questions that yield a TQOL as well as 5 subscale scores: symptoms, activities of daily living (ADLs), large fiber neuropathy/physical functioning, small fiber neuropathy, and autonomic neuropathy. TQOL score: sum of all items, total possible score range= -2 to 138, where higher score=worse QOL. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline of B3461020 (Fx-005), Month 30

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	36		
Units: units on a scale				
least squares mean (standard error)	0.1 (± 3.3)	4.5 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Change From B3461020 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 66

End point title	Val30Met Group: Change From B3461020 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 66[17][18]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire; assessed impact of DN on health related QOL of subjects with DN. Scoring was based on 35 questions that yield a TQOL as well as 5 subscale scores: symptoms, activities of daily living (ADLs), large fiber neuropathy/physical functioning, small fiber neuropathy, and autonomic neuropathy. TQOL score: sum of all items, total possible score range= -2 to 138, where higher score=worse QOL. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline of B3461020 (Fx-005), Month 66

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: units on a scale				
least squares mean (standard error)	5.2 (± 3.4)	5.3 (± 3.5)		

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Total Quality of Life (TQOL) Score Assessed Using

Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Baseline

End point title	NonVal30Met Group: Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Baseline[19][20]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire; assessed impact of DN on health related QOL of subjects with DN. Scoring was based on 35 questions that yield a TQOL as well as 5 subscale scores: symptoms, activities of daily living (ADLs), large fiber neuropathy/physical functioning, small fiber neuropathy, and autonomic neuropathy. TQOL score: sum of all items, total possible score range= -2 to 138, where higher score=worse QOL. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure.

End point type	Primary

End point timeframe:

Baseline of B3461022 (Fx1A-201)

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
arithmetic mean (standard deviation)	53.9 (± 34.2)			

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Change From B3461022 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 12

End point title	NonVal30Met Group: Change From B3461022 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 12[21][22]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire; assessed impact of DN on health related QOL of subjects with DN. Scoring was based on 35 questions that yield a TQOL as well as 5 subscale scores: symptoms, activities of daily living (ADLs), large fiber neuropathy/physical functioning, small fiber neuropathy, and autonomic neuropathy. TQOL score: sum of all items, total possible score range= -2 to 138, where higher score=worse QOL. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure.

End point type	Primary

End point timeframe:

Baseline of B3461022 (Fx1A-201), Month 12

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
least squares mean (standard error)	0.9 (± 5.7)			

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Change From B3461022 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 60

End point title	NonVal30Met Group: Change From B3461022 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 60[23][24]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire; assessed impact of DN on health related QOL of subjects with DN. Scoring was based on 35 questions that yield a TQOL as well as 5 subscale scores: symptoms, activities of daily living (ADLs), large fiber neuropathy/physical functioning, small fiber neuropathy, and autonomic neuropathy. TQOL score: sum of all items, total possible score range= -2 to 138, where higher score=worse QOL. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline of B3461022 (Fx1A-201), Month 60

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: units on a scale				
least squares mean (standard error)	12.9 (± 7.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Karnofsky Performance Scale (KPS) Score at Month 30

End point title	Val30Met Group: Karnofsky Performance Scale (KPS) Score at Month 30[25][26]

End point description:

KPS:used for rating subject ADLs on 11-step scale from 0-100, higher score=subject is better able to carry out daily activities. Score range: 100=normal no complaints; no disease evidence, 90=able to carry normal activity; minor signs/symptoms of disease, 80=normal activity with effort; some signs/symptoms, 70=cares for self; unable to carry on normal activity, 60=requires occasional assistance, but able to care for most personal needs, 50=requires considerable assistance and frequent medical care, 40=disabled; requires special care, assistance, 30=severely disabled; hospital admission indicated, death not imminent, 20=very sick; hospital admission necessary, 10=moribund; fatal processes progressing rapidly and 0=dead. Lower the score worse is survival for most serious illnesses. Data for KPS score was not collected in parent studies Fx-005 and Fx-006, not reported for any time points from parent studies. ITT population was analysed. "N"=subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Month 30 (Baseline of B3461023)

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	36		
Units: units on a scale				
arithmetic mean (standard deviation)	83.8 (± 12.99)	80.3 (± 11.83)		

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Karnofsky Performance Scale (KPS) Score at Month 66

End point title	Val30Met Group: Karnofsky Performance Scale (KPS) Score at Month 66[27][28]

End point description:

KPS:used for rating subject ADLs on 11-step scale from 0-100, higher score=subject is better able to

carry out daily activities. Score range: 100=normal no complaints; no disease evidence, 90=able to carry normal activity; minor signs/symptoms of disease, 80=normal activity with effort; some signs/symptoms, 70=cares for self; unable to carry on normal activity, 60=requires occasional assistance, but able to care for most personal needs, 50=requires considerable assistance and frequent medical care, 40=disabled; requires special care, assistance, 30=severely disabled; hospital admission indicated, death not imminent, 20=very sick; hospital admission necessary, 10=moribund; fatal processes progressing rapidly and 0=dead. Lower the score worse is survival for most serious illnesses. Data for KPS score was not collected in parent studies Fx-005 and Fx-006, not reported for any time points from parent studies. ITT population was analysed. "N"=subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Month 66 (Month 36 of B3461023)

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	31		
Units: units on a scale				
arithmetic mean (standard deviation)	85.9 (± 10.76)	78.7 (± 17.65)		

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Karnofsky Performance Scale (KPS) Score at Baseline

End point title	NonVal30Met Group: Karnofsky Performance Scale (KPS) Score at Baseline[29][30]

End point description:

KPS: used for rating subject ADLs. It rated subject on 11-step scale ranged from 0-100, higher score=subject is better able to carry out daily activities. The lower the score, the worse the survival for most serious illnesses. Score range: 100=normal no complaints; no evidence of disease, 90=able to carry on normal activity; minor signs/symptoms of disease, 80=normal activity with effort; some signs or symptoms, 70=cares for self; unable to carry on normal activity or to do active work, 60=requires occasional assistance, but able to care for most personal needs, 50=requires considerable assistance and frequent medical care, 40=disabled; requires special care and assistance, 30=severely disabled; hospital admission is indicated although death not imminent, 20=very sick; hospital admission necessary, 10=moribund; fatal processes progressing rapidly and 0=dead, where lower score=worse survival for most serious illnesses. ITT population was analysed.

End point type	Primary

End point timeframe:

Baseline of B3461022 (Fx1A-201)

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
arithmetic mean (standard deviation)	72.2 (± 13.53)			

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Change From B3461022 Baseline in Karnofsky Performance Scale (KPS) Score at Month 12

End point title	NonVal30Met Group: Change From B3461022 Baseline in Karnofsky Performance Scale (KPS) Score at Month 12[31][32]

End point description:

KPS: used for rating subject ADLs. It rated subject on 11-step scale ranged from 0-100, higher score=subject is better able to carry out daily activities. The lower the score, the worse the survival for most serious illnesses. Score range: 100=normal no complaints; no evidence of disease, 90=able to carry on normal activity; minor signs/symptoms of disease, 80=normal activity with effort; some signs or symptoms, 70=cares for self; unable to carry on normal activity or to do active work, 60=requires occasional assistance, but able to care for most personal needs, 50=requires considerable assistance and frequent medical care, 40=disabled; requires special care and assistance, 30=severely disabled; hospital admission is indicated although death not imminent, 20=very sick; hospital admission necessary, 10=moribund; fatal processes progressing rapidly and 0=dead, where lower score=worse survival for most serious illnesses. ITT population was analysed.

End point type	Primary

End point timeframe:

Baseline of B3461022 (Fx1A-201), Month 12

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
least squares mean (standard error)	-3.1 (± 2.57)			

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Change From B3461022 Baseline in Karnofsky Performance Scale (KPS) Score at Month 60

End point title	NonVal30Met Group: Change From B3461022 Baseline in Karnofsky Performance Scale (KPS) Score at Month 60[33][34]

End point description:

KPS:used for rating subject ADLs. It rated subject on 11-step scale ranged from 0-100, higher score=subject is better able to carry out daily activities. The lower the score, the worse the survival for most serious illnesses. Score range: 100=normal no complaints; no evidence of disease, 90=able to carry on normal activity; minor signs/symptoms of disease, 80=normal activity with effort; some signs or symptoms, 70=cares for self; unable to carry on normal activity or to do active work, 60=requires occasional assistance, but able to care for most personal needs, 50=requires considerable assistance and frequent medical care, 40=disabled; requires special care and assistance, 30=severely disabled; hospital admission is indicated although death not imminent, 20=very sick; hospital admission necessary, 10=moribund; fatal processes progressing rapidly and 0=dead, where lower score=worse survival for most serious illnesses. ITT population analysed. "N"=subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline of B3461022 (Fx1A-201), Month 60

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: units on a scale				
least squares mean (standard error)	-12.4 (± 3.73)			

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Number of Subjects by Ambulation Stage at Baseline

End point title	Val30Met Group: Number of Subjects by Ambulation Stage at Baseline[35][36]

End point description:

Ambulatory status for each Val30Met subject was collected using ambulatory data collection forms in [Fx-005 (B3461020), Fx-006 (B3461021)] or forms based on modified polyneuropathy disability (mPND) score in B3461023 (after protocol amendment 1.1). The data were categorised to 3 ambulation stages: Stage 1 (normal), Stage 2 (some assistance required), or Stage 3 (not ambulatory). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline of B3461020 (Fx-005)

Notes:

[35] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	36		
Units: subjects				
Stage 1 (Normal)	37	36		
Stage 2 (Some assistance required)	0	0		
Stage 3 (Not ambulatory)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Number of Subjects by Ambulation Stage at Month 30

End point title	Val30Met Group: Number of Subjects by Ambulation Stage at Month 30[37][38]

End point description:

Ambulatory status for each Val30Met subject was collected using ambulatory data collection forms in [Fx-005 (B3461020), Fx-006 (B3461021)] or forms based on mPND score in B3461023 (after protocol amendment 1.1). The data were categorised to 3 ambulation stages: Stage 1 (normal), Stage 2 (some assistance required), or Stage 3 (not ambulatory). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Month 30

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: subjects				
Stage 1 (Normal)	37	34		
Stage 2 (Some assistance required)	0	1		
Stage 3 (Not ambulatory)	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Val30Met Group: Number of Subjects by Ambulation Stage at Month 66

End point title	Val30Met Group: Number of Subjects by Ambulation Stage at Month 66[39][40]

End point description:

Ambulatory status for each Val30Met subject was collected using ambulatory data collection forms in [Fx-005 (B3461020), Fx-006 (B3461021)] or forms based on mPND score in B3461023 (after protocol amendment 1.1). The data were categorised to 3 ambulation stages: Stage 1 (normal), Stage 2 (some assistance required), or Stage 3 (not ambulatory). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Month 66

Notes:

[39] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	18		
Units: subjects				
Stage 1 (Normal)	22	15		
Stage 2 (Some assistance required)	2	3		
Stage 3 (Not ambulatory)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Number of Subjects by Ambulation Stage at Baseline

End point title	NonVal30Met Group: Number of Subjects by Ambulation Stage at Baseline[41][42]

End point description:

Ambulatory status for each Val30Met subject was collected using ambulatory data collection forms in [Fx-005 (B3461020), Fx-006 (B3461021)] or forms based on mPND score in B3461023 (after protocol amendment 1.1). The data were categorised to 3 ambulation stages: Stage 1 (normal), Stage 2 (some

assistance required), or Stage 3 (not ambulatory). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline of B3461022 (Fx1A-201)

Notes:

[41] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: subjects				
Stage 1 (Normal)	7			
Stage 2 (Some assistance required)	5			
Stage 3 (Not ambulatory)	0			

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Number of Subjects by Ambulation Stage at Month 12

End point title	NonVal30Met Group: Number of Subjects by Ambulation Stage at Month 12[43][44]

End point description:

Ambulatory status for each Val30Met subject was collected using ambulatory data collection forms in [Fx-005 (B3461020), Fx-006 (B3461021)] or forms based on mPND score in B3461023 (after protocol amendment 1.1). The data were categorised to 3 ambulation stages: Stage 1 (normal), Stage 2 (some assistance required), or Stage 3 (not ambulatory). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Month 12

Notes:

[43] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects				
Stage 1 (Normal)	7			
Stage 2 (Some assistance required)	5			
Stage 3 (Not ambulatory)	1			

Statistical analyses

No statistical analyses for this end point

Primary: NonVal30Met Group: Number of Subjects by Ambulation Stage at Month 60

End point title	NonVal30Met Group: Number of Subjects by Ambulation Stage at Month 60[45][46]

End point description:

Ambulatory status for each Val30Met subject was collected using ambulatory data collection forms in [Fx-005 (B3461020), Fx-006 (B3461021)] or forms based on mPND score in B3461023 (after protocol amendment 1.1). The data were categorised to 3 ambulation stages: Stage 1 (normal), Stage 2 (some assistance required), or Stage 3 (not ambulatory). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "N" signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Month 60

Notes:

[45] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was planned for this endpoint.

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: subjects				
Stage 1 (Normal)	1			
Stage 2 (Some assistance required)	6			
Stage 3 (Not ambulatory)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Val30Met Group: Change From B3461020 Baseline in NIS-LL Score at Month 6, 12, 18, 24, 42, 54, 78, 90, 102, 114 and 126

End point title	Val30Met Group: Change From B3461020 Baseline in NIS-LL Score at Month 6, 12, 18, 24, 42, 54, 78, 90, 102, 114 and 126[47]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. Total possible NIS-LL score range 0-88, high score=more impairment. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461020 (Fx-005), Month 6, 12, 18, 24, 42, 54, 78, 90, 102, 114 and 126

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: units on a scale				
least squares mean (standard error)				
NIS-LL: Change at Month 6 (n= 38, 37)	1.4 (± 1.5)	0.6 (± 1.5)		
NIS-LL: Change at Month 12 (n= 38, 37)	1.4 (± 1.5)	3.6 (± 1.5)		
NIS-LL: Change at Month 18 (n= 38, 37)	2.6 (± 1.5)	4.4 (± 1.5)		
NIS-LL: Change at Month 24 (n= 38, 37)	3.4 (± 1.5)	6.1 (± 1.5)		
NIS-LL: Change at Month 42 (n= 37, 35)	4.5 (± 1.5)	8.9 (± 1.6)		
NIS-LL: Change at Month 54 (n= 36, 34)	6.3 (± 1.5)	8.6 (± 1.6)		
NIS-LL: Change at Month 78 (n= 9, 7)	14.8 (± 2.4)	9.8 (± 2.6)		
NIS-LL: Change at Month 90 (n= 9, 6)	17.1 (± 2.4)	8.6 (± 2.8)		
NIS-LL: Change at Month 102 (n= 6, 5)	26.0 (± 2.8)	12.5 (± 3.0)		
NIS-LL: Change at Month 114 (n= 4, 4)	22.0 (± 3.3)	14.2 (± 3.3)		
NIS-LL: Change at Month 126 (n= 2, 2)	36.4 (± 4.6)	12.6 (± 4.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Val30Met Group: NIS-LL Subscales Scores: Muscle Weakness (MW), MW-Hip, MW-Knee, MW-Ankle, MW-Toe, NIS-LL Reflexes, NIS-LL Sensory at Baseline

End point title	Val30Met Group: NIS-LL Subscales Scores: Muscle Weakness (MW), MW-Hip, MW-Knee, MW-Ankle, MW-Toe, NIS-LL Reflexes, NIS-LL Sensory at Baseline[48]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs with a total possible NIS-LL score range of 0 to 88, higher score=greater impairment. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. NIS-LL Muscle Weakness score range is 0 to 64, high score=more impairment. NIS-LL Sensation score range is 0 to 16, high score=more impairment. NIS-LL Reflexes score range is 0 to 8, high score=more impairment. ITT population was analysed.

End point type	Secondary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461020 (Fx-005)

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: units on a scale				
arithmetic mean (standard deviation)				
NIS-LL MW: Baseline	2.1 (± 6.4)	4.2 (± 9.6)		
NIS-LL MW-Hip: Baseline	0.2 (± 0.8)	0.3 (± 1.1)		
NIS-LL MW-Knee: Baseline	0.2 (± 0.9)	0.4 (± 1.5)		
NIS-LL MW-Ankle: Baseline	0.4 (± 1.5)	1.3 (± 3.7)		
NIS-LL MW-Toe: Baseline	1.3 (± 3.6)	2.2 (± 4.2)		
NIS-LL Reflexes: Baseline	0.8 (± 1.8)	1.8 (± 2.4)		
NIS-LL Sensory: Baseline	3.9 (± 3.7)	5.6 (± 3.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Val30Met Group: Change From B3461020 Baseline in NIS-LL Subscales Scores: Muscle Weakness (MW), MW-Hip, MW-Knee, MW-Ankle, MW-Toe, NIS-LL Reflexes, NIS-LL Sensory at Month 6, 12, 18, 24, 30, 42, 54, 66, 78, 90, 102, 114 and 126

End point title	Val30Met Group: Change From B3461020 Baseline in NIS-LL Subscales Scores: Muscle Weakness (MW), MW-Hip, MW-Knee, MW-Ankle, MW-Toe, NIS-LL Reflexes, NIS-LL Sensory at Month 6, 12, 18, 24, 30, 42, 54, 66, 78, 90, 102, 114 and 126[49]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess MW, reflexes, sensation; scored separately for left, right limbs with a total possible NIS-LL score range of 0 to 88, higher score=greater impairment. Components of MW (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. NIS-LL MW score range is 0 to 64, high score=more impairment. NIS-LL Sensation score range is 0 to 16, high score=more impairment. NIS-LL

Reflexes score range is 0 to 8, high score=more impairment. ITT population was analysed. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:
Baseline (i.e. last measurement prior to first dose) of B3461020 (Fx-005), Month 6, 12, 18, 24, 30, 42, 54, 66, 78, 90, 102, 114 and 126

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: units on a scale				
least squares mean (standard error)				
NIS-LL MW: Change at Month 6 (n= 38, 37)	0.6 (± 1.2)	0.5 (± 1.2)		
NIS-LL MW: Change at Month 12 (n= 38, 37)	0.8 (± 1.2)	2.4 (± 1.2)		
NIS-LL MW: Change at Month 18 (n= 38, 37)	1.3 (± 1.2)	3.1 (± 1.2)		
NIS-LL MW: Change at Month 24 (n= 38, 37)	1.5 (± 1.2)	4.0 (± 1.2)		
NIS-LL MW: Change at Month 30 (n= 38, 36)	2.5 (± 1.2)	4.4 (± 1.2)		
NIS-LL MW: Change at Month 42 (n= 37, 35)	2.1 (± 1.2)	6.3 (± 1.2)		
NIS-LL MW: Change at Month 54 (n= 36, 34)	3.1 (± 1.2)	5.7 (± 1.2)		
NIS-LL MW: Change at Month 66 (n= 34, 31)	4.2 (± 1.2)	7.4 (± 1.2)		
NIS-LL MW: Change at Month 78 (n= 9, 7)	8.7 (± 1.9)	6.9 (± 2.1)		
NIS-LL MW: Change at Month 90 (n= 9, 6)	11.0 (± 1.9)	5.4 (± 2.2)		
NIS-LL MW: Change at Month 102 (n= 6, 5)	18.2 (± 2.2)	7.5 (± 2.4)		
NIS-LL MW: Change at Month 114 (n= 4, 4)	13.1 (± 2.6)	9.1 (± 2.6)		
NIS-LL MW: Change at Month 126 (n= 2, 2)	27.9 (± 3.6)	10.0 (± 3.6)		
NIS-LL MW-Hip: Change at Month 6 (n= 38, 37)	0.2 (± 0.3)	-0.1 (± 0.3)		
NIS-LL MW-Hip: Change at Month 12 (n= 38, 37)	0.2 (± 0.3)	0.3 (± 0.3)		
NIS-LL MW-Hip: Change at Month 18 (n= 38, 37)	0.3 (± 0.3)	0.3 (± 0.3)		
NIS-LL MW-Hip: Change at Month 24 (n= 38, 37)	0.4 (± 0.3)	0.4 (± 0.3)		
NIS-LL MW-Hip: Change at Month 30 (n= 38, 36)	0.7 (± 0.3)	0.7 (± 0.3)		
NIS-LL MW-Hip: Change at Month 42 (n= 37, 35)	0.4 (± 0.3)	0.7 (± 0.3)		
NIS-LL MW-Hip: Change at Month 54 (n= 36, 34)	0.5 (± 0.3)	0.4 (± 0.3)		

NIS-LL MW-Hip: Change at Month 66 (n= 34, 31)	0.5 (± 0.3)	0.5 (± 0.3)		
NIS-LL MW-Hip: Change at Month 78 (n= 9, 7)	0.7 (± 0.5)	0.1 (± 0.5)		
NIS-LL MW-Hip: Change at Month 90 (n= 9, 6)	0.9 (± 0.5)	0.0 (± 0.6)		
NIS-LL MW-Hip: Change at Month 102 (n= 6, 5)	2.1 (± 0.6)	0.0 (± 0.6)		
NIS-LL MW-Hip: Change at Month 114 (n= 4, 4)	0.4 (± 0.7)	0.9 (± 0.7)		
NIS-LL MW-Hip: Change at Month 126 (n= 2, 2)	2.3 (± 0.9)	2.2 (± 0.9)		
NIS-LL MW-Knee: Change at Month 6 (n= 38, 37)	0.1 (± 0.3)	0.1 (± 0.3)		
NIS-LL MW-Knee: Change at Month 12 (n= 38, 37)	0.1 (± 0.3)	0.4 (± 0.3)		
NIS-LL MW-Knee: Change at Month 18 (n= 38, 37)	0.2 (± 0.3)	0.6 (± 0.3)		
NIS-LL MW-Knee: Change at Month 24 (n= 38, 37)	0.3 (± 0.3)	0.4 (± 0.3)		
NIS-LL MW-Knee: Change at Month 30 (n= 38, 36)	0.6 (± 0.3)	0.6 (± 0.3)		
NIS-LL MW-Knee: Change at Month 42 (n= 37, 35)	0.4 (± 0.3)	0.7 (± 0.3)		
NIS-LL MW-Knee: Change at Month 54 (n= 36, 34)	0.5 (± 0.3)	0.4 (± 0.3)		
NIS-LL MW-Knee: Change at Month 66 (n= 34, 31)	0.4 (± 0.3)	0.7 (± 0.3)		
NIS-LL MW-Knee: Change at Month 78 (n= 9, 7)	0.5 (± 0.5)	1.0 (± 0.5)		
NIS-LL MW-Knee: Change at Month 90 (n= 9, 6)	1.6 (± 0.5)	0.5 (± 0.6)		
NIS-LL MW-Knee: Change at Month 102 (n= 6, 5)	5.1 (± 0.5)	1.1 (± 0.6)		
NIS-LL MW-Knee: Change at Month 114 (n= 4, 4)	0.4 (± 0.7)	1.4 (± 0.7)		
NIS-LL MW-Knee: Change at Month 126 (n= 2, 2)	3.2 (± 0.9)	3.7 (± 0.9)		
NIS-LL MW-Ankle: Change at Month 6 (n= 38, 37)	0.2 (± 0.5)	0.3 (± 0.5)		
NIS-LL MW-Ankle: Change at Month 12 (n= 38, 37)	0.4 (± 0.5)	0.7 (± 0.5)		
NIS-LL MW-Ankle: Change at Month 18 (n= 38, 37)	0.5 (± 0.5)	1.1 (± 0.5)		
NIS-LL MW-Ankle: Change at Month 24 (n= 38, 37)	0.5 (± 0.5)	1.6 (± 0.5)		
NIS-LL MW-Ankle: Change at Month 30 (n= 38, 36)	0.8 (± 0.5)	1.4 (± 0.5)		
NIS-LL MW-Ankle: Change at Month 42 (n= 37, 35)	0.8 (± 0.5)	2.3 (± 0.5)		
NIS-LL MW-Ankle: Change at Month 54 (n= 36, 34)	1.2 (± 0.5)	2.0 (± 0.5)		
NIS-LL MW-Ankle: Change at Month 66 (n= 34, 31)	1.6 (± 0.5)	2.8 (± 0.5)		
NIS-LL MW-Ankle: Change at Month 78 (n= 9, 7)	3.5 (± 0.7)	2.5 (± 0.8)		
NIS-LL MW-Ankle: Change at Month 90 (n= 9, 6)	3.9 (± 0.7)	2.6 (± 0.9)		
NIS-LL MW-Ankle: Change at Month 102 (n= 6, 5)	5.8 (± 0.9)	3.2 (± 1.0)		
NIS-LL MW-Ankle: Change at Month 114 (n= 4, 4)	5.1 (± 1.0)	3.7 (± 1.1)		

NIS-LL MW-Ankle: Change at Month 126 (n= 2, 2)	10.8 (± 1.4)	2.1 (± 1.4)	
NIS-LL MW-Toe: Change at Month 6 (n= 38, 37)	-0.1 (± 0.5)	0.3 (± 0.5)	
NIS-LL MW-Toe: Change at Month 12 (n= 38, 37)	-0.1 (± 0.5)	1.2 (± 0.5)	
NIS-LL MW-Toe: Change at Month 18 (n= 38, 37)	0.2 (± 0.5)	1.3 (± 0.5)	
NIS-LL MW-Toe: Change at Month 24 (n= 38, 37)	0.1 (± 0.5)	1.8 (± 0.5)	
NIS-LL MW-Toe: Change at Month 30 (n= 38, 36)	0.3 (± 0.5)	1.9 (± 0.5)	
NIS-LL MW-Toe: Change at Month 42 (n= 37, 35)	0.3 (± 0.5)	2.7 (± 0.5)	
NIS-LL MW-Toe: Change at Month 54 (n= 36, 34)	0.6 (± 0.5)	2.9 (± 0.5)	
NIS-LL MW-Toe: Change at Month 66 (n= 34, 31)	1.5 (± 0.5)	3.6 (± 0.5)	
NIS-LL MW-Toe: Change at Month 78 (n= 9, 7)	3.9 (± 0.8)	3.5 (± 0.9)	
NIS-LL MW-Toe: Change at Month 90 (n= 9, 6)	4.5 (± 0.8)	2.5 (± 1.0)	
NIS-LL MW-Toe: Change at Month 102 (n= 6, 5)	5.1 (± 0.9)	3.4 (± 1.0)	
NIS-LL MW-Toe: Change at Month 114 (n= 4, 4)	7.0 (± 1.1)	3.3 (± 1.1)	
NIS-LL MW-Toe: Change at Month 126 (n= 2, 2)	11.4 (± 1.5)	2.4 (± 1.5)	
NIS-LL Reflexes: Change at Month 6 (n= 38, 37)	0.2 (± 0.2)	0.1 (± 0.2)	
NIS-LL Reflexes: Change at Month 12 (n= 38, 37)	0.4 (± 0.2)	0.5 (± 0.2)	
NIS-LL Reflexes: Change at Month 18 (n= 38, 37)	0.4 (± 0.2)	0.5 (± 0.2)	
NIS-LL Reflexes: Change at Month 24 (n= 38, 37)	0.7 (± 0.2)	0.9 (± 0.2)	
NIS-LL Reflexes: Change at Month 30 (n= 38, 36)	0.5 (± 0.2)	0.7 (± 0.2)	
NIS-LL Reflexes: Change at Month 42 (n= 37, 35)	0.7 (± 0.2)	1.0 (± 0.2)	
NIS-LL Reflexes: Change at Month 54 (n= 36, 34)	0.9 (± 0.2)	1.2 (± 0.2)	
NIS-LL Reflexes: Change at Month 66 (n= 34, 31)	1.1 (± 0.2)	1.4 (± 0.2)	
NIS-LL Reflexes: Change at Month 78 (n= 9, 7)	1.5 (± 0.4)	1.3 (± 0.4)	
NIS-LL Reflexes: Change at Month 90 (n= 9, 6)	1.4 (± 0.4)	0.7 (± 0.5)	
NIS-LL Reflexes: Change at Month 102 (n= 6, 5)	2.0 (± 0.5)	1.5 (± 0.5)	
NIS-LL Reflexes: Change at Month 114 (n= 4, 4)	3.0 (± 0.6)	2.9 (± 0.6)	
NIS-LL Reflexes: Change at Month 126 (n= 2, 2)	3.6 (± 0.8)	1.1 (± 0.8)	
NIS-LL Sensory: Change at Month 6 (n= 38, 37)	0.4 (± 0.5)	0.4 (± 0.5)	
NIS-LL Sensory: Change at Month 12 (n= 38, 37)	-0.1 (± 0.5)	1.1 (± 0.5)	
NIS-LL Sensory: Change at Month 18 (n= 38, 37)	0.6 (± 0.5)	1.3 (± 0.5)	
NIS-LL Sensory: Change at Month 24 (n= 38, 37)	0.9 (± 0.5)	1.6 (± 0.5)	

NIS-LL Sensory: Change at Month 30 (n= 38, 36)	0.5 (± 0.5)	1.7 (± 0.5)		
NIS-LL Sensory: Change at Month 42 (n= 37, 35)	1.4 (± 0.5)	2.0 (± 0.5)		
NIS-LL Sensory: Change at Month 54 (n= 36, 34)	2.0 (± 0.5)	2.1 (± 0.6)		
NIS-LL Sensory: Change at Month 66 (n= 34, 31)	2.2 (± 0.5)	2.9 (± 0.6)		
NIS-LL Sensory: Change at Month 78 (n= 9, 7)	4.3 (± 0.8)	1.9 (± 0.9)		
NIS-LL Sensory: Change at Month 90 (n= 9, 6)	4.5 (± 0.8)	2.8 (± 0.9)		
NIS-LL Sensory: Change at Month 102 (n= 6, 5)	5.5 (± 0.9)	3.9 (± 1.0)		
NIS-LL Sensory: Change at Month 114 (n= 4, 4)	5.4 (± 1.1)	2.6 (± 1.1)		
NIS-LL Sensory: Change at Month 126 (n= 2, 2)	4.6 (± 1.5)	1.8 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: NonVal30Met Group: Change From B3461022 Baseline in NIS-LL Score at Month 6, 24, 36, 48, 72, 84, 96, 108 and 120

End point title	NonVal30Met Group: Change From B3461022 Baseline in NIS-LL Score at Month 6, 24, 36, 48, 72, 84, 96, 108 and 120[50]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. Total possible NIS-LL score range 0-88, high score=more impairment. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461022 (Fx1A-201), 6, 24, 36, 48, 72, 84, 96, 108 and 120

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
least squares mean (standard error)				
NIS-LL: Change at Month 6 (n= 18)	-0.7 (± 2.0)			
NIS-LL: Change at Month 24 (n= 18)	6.6 (± 2.0)			
NIS-LL: Change at Month 36 (n= 11)	10.9 (± 2.3)			

NIS-LL: Change at Month 48 (n= 10)	12.3 (± 2.4)			
NIS-LL: Change at Month 72 (n= 3)	14.6 (± 3.7)			
NIS-LL: Change at Month 84 (n= 2)	10.4 (± 4.4)			
NIS-LL: Change at Month 96 (n= 2)	13.9 (± 4.4)			
NIS-LL: Change at Month 108 (n= 2)	12.9 (± 4.4)			
NIS-LL: Change at Month 120 (n= 2)	13.9 (± 4.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: NonVal30Met Group: NIS-LL Subscales Scores: Muscle Weakness (MW), MW-Hip, MW-Knee, MW-Ankle, MW-Toe, NIS-LL Reflexes, NIS-LL Sensory at Baseline

End point title	NonVal30Met Group: NIS-LL Subscales Scores: Muscle Weakness (MW), MW-Hip, MW-Knee, MW-Ankle, MW-Toe, NIS-LL Reflexes, NIS-LL Sensory at Baseline[51]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess muscle weakness, reflexes, sensation; scored separately for left, right limbs with a total possible NIS-LL score range of 0 to 88, higher score=greater impairment. Components of muscle weakness (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. NIS-LL Muscle Weakness score range is 0 to 64, high score=more impairment. NIS-LL Sensation score range is 0 to 16, high score=more impairment. NIS-LL Reflexes score range is 0 to 8, high score=more impairment. ITT population was analysed.

End point type	Secondary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461022 (Fx1A-201)

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
arithmetic mean (standard deviation)				
NIS-LL MW: Baseline	16.6 (± 16.9)			
NIS-LL MW-Hip: Baseline	1.6 (± 2.4)			
NIS-LL MW-Knee: Baseline	2.5 (± 3.8)			
NIS-LL MW-Ankle: Baseline	5.5 (± 6.0)			
NIS-LL MW-Toe: Baseline	6.9 (± 6.6)			
NIS-LL Reflexes: Baseline	5.6 (± 3.4)			
NIS-LL Sensory: Baseline	8.9 (± 5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: NonVal30Met Group: Change From B3461022 Baseline in NIS-LL Subscales Scores: Muscle Weakness (MW), MW-Hip, MW-Knee, MW-Ankle, MW-Toe, NIS-LL Reflexes, NIS-LL Sensory at Month 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120

End point title	NonVal30Met Group: Change From B3461022 Baseline in NIS-LL Subscales Scores: Muscle Weakness (MW), MW-Hip, MW-Knee, MW-Ankle, MW-Toe, NIS-LL Reflexes, NIS-LL Sensory at Month 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120[52]

End point description:

NIS-LL: a subscale (of 37-item NIS questionnaire) that provided a total neuropathic deficit score for the lower limbs. It assess MW, reflexes, sensation; scored separately for left, right limbs with a total possible NIS-LL score range of 0 to 88, higher score=greater impairment. Components of MW (hip and knee flexion, hip and knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors) scored on scale 0 (normal) to 4 (paralysis), higher score=greater weakness. Components of reflexes (quadriceps femoris, triceps surae); sensation (touch pressure, pin-prick, vibration, joint position) scored 0=normal, 1=decreased, or 2=absent. NIS-LL MW score range is 0 to 64, high score=more impairment. NIS-LL Sensation score range is 0 to 16, high score=more impairment. NIS-LL Reflexes score range is 0 to 8, high score=more impairment. ITT population was analysed. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline (i.e. last measurement prior to first dose) of B3461022 (Fx1A-201), Month 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
least squares mean (standard error)				
NIS-LL MW: Change at Month 6 (n= 18)	-0.4 (± 1.5)			
NIS-LL MW: Change at Month 12 (n= 18)	2.3 (± 1.5)			
NIS-LL MW: Change at Month 24 (n= 18)	5.1 (± 1.5)			
NIS-LL MW: Change at Month 36 (n= 11)	7.3 (± 1.8)			
NIS-LL MW: Change at Month 48 (n= 10)	9.7 (± 1.9)			
NIS-LL MW: Change at Month 60 (n= 7)	8.0 (± 2.1)			
NIS-LL MW: Change at Month 72 (n= 3)	8.1 (± 3.0)			
NIS-LL MW: Change at Month 84 (n= 2)	5.7 (± 3.6)			
NIS-LL MW: Change at Month 96 (n= 2)	5.2 (± 3.6)			
NIS-LL MW: Change at Month 108 (n= 2)	6.2 (± 3.6)			
NIS-LL MW: Change at Month 120 (n= 2)	10.2 (± 3.6)			
NIS-LL MW-Hip: Change at Month 6 (n= 18)	-0.3 (± 0.6)			
NIS-LL MW-Hip: Change at Month 12 (n= 18)	0.6 (± 0.6)			

NIS-LL MW-Hip: Change at Month 24 (n= 18)	1.1 (± 0.6)			
NIS-LL MW-Hip: Change at Month 36 (n= 11)	0.9 (± 0.6)			
NIS-LL MW-Hip: Change at Month 48 (n= 10)	1.3 (± 0.6)			
NIS-LL MW-Hip: Change at Month 60 (n= 7)	0.0 (± 0.7)			
NIS-LL MW-Hip: Change at Month 72 (n= 3)	0.4 (± 0.9)			
NIS-LL MW-Hip: Change at Month 84 (n= 2)	1.4 (± 1.0)			
NIS-LL MW-Hip: Change at Month 96 (n= 2)	0.4 (± 1.0)			
NIS-LL MW-Hip: Change at Month 108 (n= 2)	0.4 (± 1.0)			
NIS-LL MW-Hip: Change at Month 120 (n= 2)	1.9 (± 1.0)			
NIS-LL MW-Knee: Change at Month 6 (n= 18)	0.0 (± 0.7)			
NIS-LL MW-Knee: Change at Month 12 (n= 18)	0.6 (± 0.7)			
NIS-LL MW-Knee: Change at Month 24 (n= 18)	1.3 (± 0.7)			
NIS-LL MW-Knee: Change at Month 36 (n= 11)	1.3 (± 0.8)			
NIS-LL MW-Knee: Change at Month 48 (n= 10)	1.8 (± 0.8)			
NIS-LL MW-Knee: Change at Month 60 (n= 7)	-0.2 (± 0.9)			
NIS-LL MW-Knee: Change at Month 72 (n= 3)	1.3 (± 1.1)			
NIS-LL MW-Knee: Change at Month 84 (n= 2)	0.7 (± 1.3)			
NIS-LL MW-Knee: Change at Month 96 (n= 2)	0.7 (± 1.3)			
NIS-LL MW-Knee: Change at Month 108 (n= 2)	0.7 (± 1.3)			
NIS-LL MW-Knee: Change at Month 120 (n= 2)	0.7 (± 1.3)			
NIS-LL MW-Ankle: Change at Month 6 (n= 18)	-0.2 (± 0.6)			
NIS-LL MW-Ankle: Change at Month 12 (n= 18)	0.7 (± 0.6)			
NIS-LL MW-Ankle: Change at Month 24 (n= 18)	1.5 (± 0.6)			
NIS-LL MW-Ankle: Change at Month 36 (n= 11)	2.7 (± 0.7)			
NIS-LL MW-Ankle: Change at Month 48 (n= 10)	3.3 (± 0.7)			
NIS-LL MW-Ankle: Change at Month 60 (n= 7)	4.6 (± 0.8)			
NIS-LL MW-Ankle: Change at Month 72 (n= 3)	2.8 (± 1.2)			
NIS-LL MW-Ankle: Change at Month 84 (n= 2)	2.0 (± 1.4)			
NIS-LL MW-Ankle: Change at Month 96 (n= 2)	2.0 (± 1.4)			
NIS-LL MW-Ankle: Change at Month 108 (n= 2)	2.0 (± 1.4)			
NIS-LL MW-Ankle: Change at Month 120 (n= 2)	2.0 (± 1.4)			

NIS-LL MW-Toe: Change at Month 6 (n= 18)	0.5 (± 0.7)			
NIS-LL MW-Toe: Change at Month 12 (n= 18)	0.8 (± 0.7)			
NIS-LL MW-Toe: Change at Month 24 (n= 18)	1.5 (± 0.7)			
NIS-LL MW-Toe: Change at Month 36 (n= 11)	2.6 (± 0.8)			
NIS-LL MW-Toe: Change at Month 48 (n= 10)	3.5 (± 0.8)			
NIS-LL MW-Toe: Change at Month 60 (n= 7)	3.9 (± 0.9)			
NIS-LL MW-Toe: Change at Month 72 (n= 3)	3.8 (± 1.3)			
NIS-LL MW-Toe: Change at Month 84 (n= 2)	1.7 (± 1.6)			
NIS-LL MW-Toe: Change at Month 96 (n= 2)	2.2 (± 1.6)			
NIS-LL MW-Toe: Change at Month 108 (n= 2)	3.2 (± 1.6)			
NIS-LL MW-Toe: Change at Month 120 (n= 2)	5.7 (± 1.6)			
NIS-LL Reflexes: Change at Month 6 (n= 18)	-0.1 (± 0.4)			
NIS-LL Reflexes: Change at Month 12 (n= 18)	-0.2 (± 0.4)			
NIS-LL Reflexes: Change at Month 24 (n= 18)	0.8 (± 0.4)			
NIS-LL Reflexes: Change at Month 36 (n= 11)	1.6 (± 0.5)			
NIS-LL Reflexes: Change at Month 48 (n= 10)	1.1 (± 0.5)			
NIS-LL Reflexes: Change at Month 60 (n= 7)	0.7 (± 0.6)			
NIS-LL Reflexes: Change at Month 72 (n= 3)	2.3 (± 0.9)			
NIS-LL Reflexes: Change at Month 84 (n= 2)	1.8 (± 1.1)			
NIS-LL Reflexes: Change at Month 96 (n= 2)	2.3 (± 1.1)			
NIS-LL Reflexes: Change at Month 108 (n= 2)	2.3 (± 1.1)			
NIS-LL Reflexes: Change at Month 120 (n= 2)	-2.2 (± 1.1)			
NIS-LL Sensory: Change at Month 6 (n= 18)	-0.1 (± 0.7)			
NIS-LL Sensory: Change at Month 12 (n= 18)	0.4 (± 0.7)			
NIS-LL Sensory: Change at Month 24 (n= 18)	0.9 (± 0.7)			
NIS-LL Sensory: Change at Month 36 (n= 11)	2.1 (± 0.8)			
NIS-LL Sensory: Change at Month 48 (n= 10)	1.7 (± 0.8)			
NIS-LL Sensory: Change at Month 60 (n= 7)	3.4 (± 0.9)			
NIS-LL Sensory: Change at Month 72 (n= 3)	4.2 (± 1.2)			
NIS-LL Sensory: Change at Month 84 (n= 2)	2.9 (± 1.4)			
NIS-LL Sensory: Change at Month 96 (n= 2)	6.4 (± 1.4)			

NIS-LL Sensory: Change at Month 108 (n= 2)	4.4 (± 1.4)			
NIS-LL Sensory: Change at Month 120 (n= 2)	5.9 (± 1.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Val30Met Group: Change From B3461020 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 6, 12, 18, 24, 42, 54, 78, 90, 102, 114, 126, 138

End point title	Val30Met Group: Change From B3461020 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 6, 12, 18, 24, 42, 54, 78, 90, 102, 114, 126, 138[53]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire; assessed impact of DN on health related QOL of subjects with DN. Scoring was based on 35 questions that yield a TQOL as well as 5 subscale scores: symptoms, activities of daily living (ADLs), large fiber neuropathy/physical functioning, small fiber neuropathy, and autonomic neuropathy. TQOL score: sum of all items, total possible score range= -2 to 138, where higher score=worse QOL. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline of B3461020 (Fx-005), Month 6, 12, 18, 24, 42, 54, 78, 90, 102, 114, 126, 138

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: units on a scale				
least squares mean (standard error)				
TQOL: Change at Month 6 (n= 38, 36)	-2.2 (± 3.3)	-0.5 (± 3.4)		
TQOL: Change at Month 12 (n= 38, 36)	-2.8 (± 3.3)	5.4 (± 3.4)		
TQOL: Change at Month 18 (n= 38, 36)	-2.3 (± 3.3)	6.4 (± 3.4)		
TQOL: Change at Month 24 (n= 38, 36)	-3.2 (± 3.3)	2.0 (± 3.4)		
TQOL: Change at Month 42 (n= 36, 33)	3.2 (± 3.3)	1.8 (± 3.4)		
TQOL: Change at Month 54 (n= 36, 33)	3.0 (± 3.3)	2.1 (± 3.4)		
TQOL: Change at Month 78 (n= 9, 6)	7.0 (± 4.8)	-3.9 (± 5.6)		
TQOL: Change at Month 90 (n= 7, 5)	3.2 (± 5.2)	-2.0 (± 6.0)		
TQOL: Change at Month 102 (n= 5, 4)	15.8 (± 5.9)	-7.3 (± 6.5)		
TQOL: Change at Month 114 (n= 4, 4)	18.9 (± 6.5)	-9.0 (± 6.5)		
TQOL: Change at Month 126 (n= 2, 2)	48.1 (± 8.7)	2.0 (± 8.7)		
TQOL: Change at Month 138 (n= 1, 1)	55.4 (± 12.0)	26.0 (± 12.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Val30Met Group: TQOL Subscale Scores: Symptom, ADLs, Physical Functioning/Large Fiber Neuropathy, Small Fiber Neuropathy, Autonomic Neuropathy Assessed Using Norfolk QOL-DN at Baseline

End point title	Val30Met Group: TQOL Subscale Scores: Symptom, ADLs, Physical Functioning/Large Fiber Neuropathy, Small Fiber Neuropathy, Autonomic Neuropathy Assessed Using Norfolk QOL-DN at Baseline[54]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire to assess impact of DN on QOL; Item 1 to 7: scored as 1=symptom present, 0=symptom absent. Items 8 to 35: scored on 5-point Likert scale: 0=no problem to 4=severe problem (except item 32, where -1="somewhat better", -2=much better, 0=about the same, 1=somewhat worse, 2=much worse). Norfolk QOL-DN summarised in 5 domains (score range): physical functioning/large fiber neuropathy (PF/LFN) (-2 to 58), activities of daily living (ADLs) (0 to 20), symptoms (0 to 32), small fiber neuropathy (SFN) (0 to 16), autonomic neuropathy (AN) (0 to 12); higher score=greater impairment, for each. Total score= -2 to 138 (higher score=worse QOL). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline of B3461020 (Fx-005)

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: units on a scale				
arithmetic mean (standard deviation)				
Symptom: Baseline (n= 38, 36)	6.4 (± 5.4)	6.8 (± 6.5)		
ADLs: Baseline (n= 38, 36)	1.4 (± 3.5)	1.9 (± 4.6)		
PF/LFN: Baseline (n= 38, 36)	12.4 (± 14.4)	15.9 (± 15.9)		
SFN: Baseline (n= 38, 36)	1.8 (± 3.2)	3.1 (± 4.2)		
AN: Baseline (n= 38, 36)	2.1 (± 2.8)	2.2 (± 2.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Val30Met:Change From Baseline in TQOL Subscale Scores:Symptom, ADLs, Physical Functioning/Large Fiber Neuropathy, Small Fiber Neuropathy, Autonomic Neuropathy Assessed Using Norfolk QOL-DN at Month 6, 12, 18, 24, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138

End point title	Val30Met:Change From Baseline in TQOL Subscale Scores:Symptom, ADLs, Physical Functioning/Large Fiber Neuropathy, Small Fiber Neuropathy, Autonomic Neuropathy Assessed Using Norfolk QOL-DN at Month 6, 12, 18, 24, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138[55]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire to assess impact of DN on QOL; Item 1 to 7: scored as 1=symptom present, 0=symptom absent. Items 8 to 35: scored on 5-point Likert scale: 0=no problem to 4=severe problem (except item 32, where -1="somewhat better", -2=much better, 0=about the same, 1=somewhat worse, 2=much worse). Norfolk QOL-DN summarised in 5 domains (score range): physical functioning/large fiber neuropathy (PF/LFN) (-2 to 58), activities of daily living (ADLs) (0 to 20), symptoms (0 to 32), small fiber neuropathy (SFN) (0 to 16), autonomic neuropathy (AN) (0 to 12); higher score=greater impairment, for each. Total score= -2 to 138 (higher score=worse QOL). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline of B3461020 (Fx-005), Month 6, 12, 18, 24, 30, 42, 54, 66, 78, 90, 102, 114, 126 and 138

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: units on a scale				
least squares mean (standard error)				
Symptom: Change at Month 6 (n= 38, 36)	-0.2 (± 0.8)	-0.1 (± 0.8)		
Symptom: Change at Month 12 (n= 38, 36)	-0.9 (± 0.8)	1.5 (± 0.8)		
Symptom: Change at Month 18 (n= 38, 36)	-1.1 (± 0.8)	0.6 (± 0.8)		
Symptom: Change at Month 24 (n= 37, 36)	-1.1 (± 0.8)	0.1 (± 0.8)		
Symptom: Change at Month 30 (n= 37, 36)	-1.4 (± 0.8)	-0.7 (± 0.8)		
Symptom: Change at Month 42 (n= 36, 33)	-0.4 (± 0.8)	-0.9 (± 0.8)		
Symptom: Change at Month 54 (n= 36, 33)	-0.3 (± 0.8)	0.2 (± 0.8)		
Symptom: Change at Month 66 (n= 33, 31)	0.6 (± 0.8)	-0.4 (± 0.8)		
Symptom: Change at Month 78 (n= 9, 6)	0.0 (± 1.2)	-2.8 (± 1.5)		
Symptom: Change at Month 90 (n= 7, 5)	1.0 (± 1.4)	-2.0 (± 1.6)		
Symptom: Change at Month 102 (n= 5, 4)	-0.7 (± 1.6)	-2.8 (± 1.7)		
Symptom: Change at Month 114 (n= 4, 4)	1.9 (± 1.7)	-3.5 (± 1.7)		

Symptom: Change at Month 126 (n= 2, 2)	5.7 (± 2.4)	-1.3 (± 2.4)		
Symptom: Change at Month 138 (n= 1, 1)	4.1 (± 3.3)	3.9 (± 3.3)		
ADLs: Change at Month 6 (n= 38, 36)	0.0 (± 0.6)	0.2 (± 0.6)		
ADLs: Change at Month 12 (n= 38, 36)	0.7 (± 0.6)	0.9 (± 0.6)		
ADLs: Change at Month 18 (n= 38, 36)	1.0 (± 0.6)	1.3 (± 0.6)		
ADLs: Change at Month 24 (n= 38, 36)	0.7 (± 0.6)	1.0 (± 0.6)		
ADLs: Change at Month 30 (n= 37, 36)	1.1 (± 0.6)	1.2 (± 0.6)		
ADLs: Change at Month 42 (n= 36, 33)	1.5 (± 0.6)	1.4 (± 0.6)		
ADLs: Change at Month 54 (n= 36, 33)	0.9 (± 0.6)	1.1 (± 0.6)		
ADLs: Change at Month 66 (n= 33, 31)	1.5 (± 0.6)	2.0 (± 0.6)		
ADLs: Change at Month 78 (n= 9, 6)	2.3 (± 0.9)	1.2 (± 1.0)		
ADLs: Change at Month 90 (n= 7, 5)	1.7 (± 0.9)	0.6 (± 1.1)		
ADLs: Change at Month 102 (n= 5, 4)	5.6 (± 1.1)	-0.8 (± 1.2)		
ADLs: Change at Month 114 (n= 4, 4)	5.6 (± 1.2)	-0.3 (± 1.2)		
ADLs: Change at Month 126 (n= 2, 2)	7.5 (± 1.6)	1.5 (± 1.6)		
ADLs: Change at Month 138 (n= 1, 1)	12.8 (± 2.2)	7.2 (± 2.2)		
PF/LFN: Change at Month 6 (n= 38, 36)	-2.3 (± 1.7)	-1.0 (± 1.7)		
PF/LFN: Change at Month 12 (n= 38, 36)	-2.9 (± 1.7)	1.0 (± 1.7)		
PF/LFN: Change at Month 18 (n= 38, 36)	-2.7 (± 1.7)	2.7 (± 1.7)		
PF/LFN: Change at Month 24 (n= 38, 36)	-3.2 (± 1.7)	-0.5 (± 1.7)		
PF/LFN: Change at Month 30 (n= 37, 36)	-1.0 (± 1.7)	1.9 (± 1.7)		
PF/LFN: Change at Month 42 (n= 36, 33)	0.6 (± 1.7)	-0.1 (± 1.8)		
PF/LFN: Change at Month 54 (n= 36, 33)	0.8 (± 1.7)	-0.4 (± 1.8)		
PF/LFN: Change at Month 66 (n= 33, 31)	1.3 (± 1.7)	2.1 (± 1.8)		
PF/LFN: Change at Month 78 (n= 9, 6)	2.6 (± 2.5)	-2.6 (± 2.9)		
PF/LFN: Change at Month 90 (n= 7, 5)	-0.7 (± 2.8)	0.1 (± 3.2)		
PF/LFN: Change at Month 102 (n= 5, 4)	7.0 (± 3.1)	-3.6 (± 3.5)		
PF/LFN: Change at Month 114 (n= 4, 4)	7.2 (± 3.5)	-4.1 (± 3.5)		
PF/LFN: Change at Month 126 (n= 2, 2)	24.8 (± 4.7)	1.8 (± 4.7)		
PF/LFN: Change at Month 138 (n= 1, 1)	24.7 (± 6.5)	8.9 (± 6.5)		
SFN: Change at Month 6 (n= 38, 36)	0.2 (± 0.5)	0.5 (± 0.5)		
SFN: Change at Month 12 (n= 38, 36)	0.5 (± 0.5)	1.8 (± 0.5)		
SFN: Change at Month 18 (n= 38, 36)	0.4 (± 0.5)	1.5 (± 0.5)		
SFN: Change at Month 24 (n= 38, 36)	0.3 (± 0.5)	1.6 (± 0.5)		
SFN: Change at Month 30 (n= 37, 36)	1.1 (± 0.5)	2.0 (± 0.5)		
SFN: Change at Month 42 (n= 36, 33)	1.7 (± 0.5)	2.2 (± 0.5)		
SFN: Change at Month 54 (n= 36, 33)	1.9 (± 0.5)	1.6 (± 0.5)		
SFN: Change at Month 66 (n= 33, 31)	1.9 (± 0.5)	1.8 (± 0.5)		
SFN: Change at Month 78 (n= 9, 6)	1.9 (± 0.8)	1.3 (± 0.9)		
SFN: Change at Month 90 (n= 7, 5)	1.7 (± 0.9)	1.1 (± 1.0)		
SFN: Change at Month 102 (n= 5, 4)	3.0 (± 1.0)	1.2 (± 1.1)		
SFN: Change at Month 114 (n= 4, 4)	2.8 (± 1.1)	1.2 (± 1.1)		
SFN: Change at Month 126 (n= 2, 2)	8.3 (± 1.4)	1.1 (± 1.5)		
SFN: Change at Month 138 (n= 1, 1)	11.8 (± 2.0)	6.8 (± 2.0)		
AN: Change at Month 6 (n= 38, 36)	-0.1 (± 0.3)	0.0 (± 0.4)		
AN: Change at Month 12 (n= 38, 36)	-0.3 (± 0.3)	0.3 (± 0.4)		

AN: Change at Month 18 (n= 38, 36)	0.0 (± 0.3)	0.5 (± 0.4)		
AN: Change at Month 24 (n= 38, 36)	-0.2 (± 0.3)	0.0 (± 0.4)		
AN: Change at Month 30 (n= 37, 36)	0.2 (± 0.3)	0.2 (± 0.4)		
AN: Change at Month 42 (n= 36, 33)	-0.3 (± 0.3)	-0.7 (± 0.4)		
AN: Change at Month 54 (n= 36, 33)	-0.5 (± 0.3)	-0.4 (± 0.4)		
AN: Change at Month 66 (n= 33, 31)	-0.3 (± 0.4)	-0.3 (± 0.4)		
AN: Change at Month 78 (n= 9, 6)	0.1 (± 0.6)	-1.1 (± 0.7)		
AN: Change at Month 90 (n= 7, 5)	-0.6 (± 0.6)	-1.9 (± 0.7)		
AN: Change at Month 102 (n= 5, 4)	0.8 (± 0.7)	-1.4 (± 0.8)		
AN: Change at Month 114 (n= 4, 4)	1.2 (± 0.8)	-2.4 (± 0.8)		
AN: Change at Month 126 (n= 2, 2)	1.6 (± 1.1)	-1.2 (± 1.1)		
AN: Change at Month 138 (n= 1, 1)	1.9 (± 1.5)	-0.7 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: NonVal30Met Group: Change From B3461022 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 6, 24, 36, 48, 72, 84, 96, 108, 120

End point title	NonVal30Met Group: Change From B3461022 Baseline in Total Quality of Life (TQOL) Score Assessed Using Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) Questionnaire at Month 6, 24, 36, 48, 72, 84, 96, 108, 120[56]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire; assessed impact of DN on health related QOL of subjects with DN. Scoring was based on 35 questions that yield a TQOL as well as 5 subscale scores: symptoms, activities of daily living (ADLs), large fiber neuropathy/physical functioning, small fiber neuropathy, and autonomic neuropathy. TQOL score: sum of all items, total possible score range= -2 to 138, where higher score=worse QOL. ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline of B3461022 (Fx1A-201), Month 6, 24, 36, 48, 72, 84, 96, 108, 120

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
least squares mean (standard error)				
TQOL: Change at Month 6 (n= 17)	-4.0 (± 5.8)			
TQOL: Change at Month 24 (n= 18)	4.0 (± 5.7)			
TQOL: Change at Month 36 (n= 12)	15.8 (± 6.3)			
TQOL: Change at Month 48 (n= 9)	15.5 (± 6.9)			
TQOL: Change at Month 72 (n= 3)	16.2 (± 10.1)			
TQOL: Change at Month 84 (n= 2)	9.5 (± 11.9)			

TQOL: Change at Month 96 (n= 2)	11.5 (± 11.9)			
TQOL: Change at Month 108 (n= 2)	22.0 (± 11.9)			
TQOL: Change at Month 120 (n= 2)	28.5 (± 11.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: NonVal30Met Group: TQOL Subscale Scores: Symptom, ADLs, Physical Functioning/Large Fiber Neuropathy, Small Fiber Neuropathy, Autonomic Neuropathy Assessed Using Norfolk QOL-DN at Baseline

End point title	NonVal30Met Group: TQOL Subscale Scores: Symptom, ADLs, Physical Functioning/Large Fiber Neuropathy, Small Fiber Neuropathy, Autonomic Neuropathy Assessed Using Norfolk QOL-DN at Baseline[57]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire to assess impact of DN on QOL; Item 1 to 7: scored as 1=symptom present, 0=symptom absent. Items 8 to 35: scored on 5-point Likert scale: 0=no problem to 4=severe problem (except item 32, where -1="somewhat better", -2=much better, 0=about the same, 1=somewhat worse, 2=much worse). Norfolk QOL-DN summarised in 5 domains (score range): physical functioning/large fiber neuropathy (-2 to 58), activities of daily living (ADLs) (0 to 20), symptoms (0 to 32), small fiber neuropathy (0 to 16), autonomic neuropathy (0 to 12); higher score=greater impairment, for each. Total score= -2 to 138 (higher score=worse QOL). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure.

End point type	Secondary

End point timeframe:

Baseline of B3461022 (Fx1A-201)

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
arithmetic mean (standard deviation)				
Symptom: Baseline	10.3 (± 7.3)			
ADLs: Baseline	8.4 (± 6.9)			
PF/LFN: Baseline	28.7 (± 18.1)			
SFN: Baseline	4.5 (± 5.0)			
AN: Baseline	2.0 (± 2.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: NonVal30Met Group: Change From Baseline in TQOL Subscale Scores:

Symptom, ADLs, Physical Functioning/Large Fiber Neuropathy, Small Fiber Neuropathy, Autonomic Neuropathy Assessed Using Norfolk QOL-DN at Month 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120

End point title	NonVal30Met Group: Change From Baseline in TQOL Subscale Scores: Symptom, ADLs, Physical Functioning/Large Fiber Neuropathy, Small Fiber Neuropathy, Autonomic Neuropathy Assessed Using Norfolk QOL-DN at Month 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120[58]

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire to assess impact of DN on QOL; Item 1 to 7: scored as 1=symptom present, 0=symptom absent. Items 8 to 35: scored on 5-point Likert scale: 0=no problem to 4=severe problem (except item 32, where -1="somewhat better", -2=much better, 0=about the same, 1=somewhat worse, 2=much worse). Norfolk QOL-DN summarised in 5 domains (score range): physical functioning/large fiber neuropathy (-2 to 58), activities of daily living (ADLs) (0 to 20), symptoms (0 to 32), small fiber neuropathy (0 to 16), autonomic neuropathy (0 to 12); higher score=greater impairment, for each. Total score= -2 to 138 (higher score=worse QOL). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline of B3461022 (Fx1A-201), Month 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
least squares mean (standard error)				
Symptom: Change at Month 6 (n= 17)	-0.8 (± 1.1)			
Symptom: Change at Month 12 (n= 18)	0.0 (± 1.1)			
Symptom: Change at Month 24 (n= 16)	-0.1 (± 1.1)			
Symptom: Change at Month 36 (n= 10)	2.9 (± 1.3)			
Symptom: Change at Month 48 (n= 9)	4.1 (± 1.3)			
Symptom: Change at Month 60 (n= 7)	2.6 (± 1.4)			
Symptom: Change at Month 72 (n= 3)	2.5 (± 1.9)			
Symptom: Change at Month 84 (n= 2)	0.5 (± 2.3)			
Symptom: Change at Month 96 (n= 2)	1.0 (± 2.3)			
Symptom: Change at Month 108 (n= 2)	2.5 (± 2.3)			
Symptom: Change at Month 120 (n= 2)	-0.5 (± 2.3)			
ADLs: Change at Month 6 (n= 17)	0.1 (± 1.1)			
ADLs: Change at Month 12 (n= 18)	1.1 (± 1.1)			
ADLs: Change at Month 24 (n= 18)	1.8 (± 1.1)			
ADLs: Change at Month 36 (n= 12)	3.5 (± 1.2)			
ADLs: Change at Month 48 (n= 9)	3.5 (± 1.3)			
ADLs: Change at Month 60 (n= 7)	3.1 (± 1.4)			
ADLs: Change at Month 72 (n= 3)	3.4 (± 1.9)			
ADLs: Change at Month 84 (n= 2)	3.2 (± 2.3)			
ADLs: Change at Month 96 (n= 2)	3.2 (± 2.3)			
ADLs: Change at Month 108 (n= 2)	4.2 (± 2.3)			
ADLs: Change at Month 120 (n= 2)	8.2 (± 2.3)			

PF/LFN: Change at Month 6 (n= 17)	-2.1 (± 3.4)				
PF/LFN: Change at Month 12 (n= 18)	-0.6 (± 3.3)				
PF/LFN: Change at Month 24 (n= 18)	0.6 (± 3.3)				
PF/LFN: Change at Month 36 (n= 12)	7.1 (± 3.7)				
PF/LFN: Change at Month 48 (n= 9)	5.8 (± 4.0)				
PF/LFN: Change at Month 60 (n= 7)	5.5 (± 4.3)				
PF/LFN: Change at Month 72 (n= 3)	4.5 (± 5.8)				
PF/LFN: Change at Month 84 (n= 2)	2.9 (± 6.8)				
PF/LFN: Change at Month 96 (n= 2)	5.4 (± 6.8)				
PF/LFN: Change at Month 108 (n= 2)	11.4 (± 6.8)				
PF/LFN: Change at Month 120 (n= 2)	15.4 (± 6.8)				
SFN: Change at Month 6 (n= 17)	-0.4 (± 0.9)				
SFN: Change at Month 12 (n= 18)	0.9 (± 0.9)				
SFN: Change at Month 24 (n= 18)	0.9 (± 0.9)				
SFN: Change at Month 36 (n= 12)	1.6 (± 1.0)				
SFN: Change at Month 48 (n= 9)	2.2 (± 1.2)				
SFN: Change at Month 60 (n= 7)	1.5 (± 1.3)				
SFN: Change at Month 72 (n= 3)	4.1 (± 1.7)				
SFN: Change at Month 84 (n= 2)	2.1 (± 2.1)				
SFN: Change at Month 96 (n= 2)	1.6 (± 2.1)				
SFN:Change at Month 108 (n= 2)	2.6 (± 2.1)				
SFN: Change at Month 120 (n= 2)	2.1 (± 2.1)				
AN: Change at Month 6 (n= 17)	-0.5 (± 0.4)				
AN: Change at Month 12 (n= 18)	0.0 (± 0.4)				
AN: Change at Month 24 (n= 18)	0.2 (± 0.4)				
AN: Change at Month 36 (n= 12)	0.1 (± 0.4)				
AN: Change at Month 48 (n= 9)	0.3 (± 0.5)				
AN: Change at Month 60 (n= 7)	0.2 (± 0.6)				
AN: Change at Month 72 (n= 3)	1.6 (± 0.8)				
AN: Change at Month 84 (n= 2)	0.6 (± 1.0)				
AN: Change at Month 96 (n= 2)	0.1 (± 1.0)				
AN: Change at Month 108 (n= 2)	1.1 (± 1.0)				
AN: Change at Month 120 (n= 2)	3.1 (± 1.0)				

Statistical analyses

No statistical analyses for this end point

Secondary: Val30Met Group: Karnofsky Performance Scale (KPS) Score at Month 42, 54, 78, 90, 102, 114, 126 and 138

End point title	Val30Met Group: Karnofsky Performance Scale (KPS) Score at Month 42, 54, 78, 90, 102, 114, 126 and 138[59]

End point description:

KPS:used for rating subject ADLs on 11-step scale from 0-100, higher score=subject is better able to carry out daily activities. Score range: 100=normal no complaints; no disease evidence, 90=able to carry normal activity; minor signs/symptoms of disease, 80=normal activity with effort; some signs/symptoms, 70=cares for self; unable to carry on normal activity, 60=requires occasional assistance, but able to care for most personal needs, 50=requires considerable assistance and frequent medical care, 40=disabled; requires special care, assistance, 30=severely disabled; hospital admission indicated, death not imminent, 20=very sick; hospital admission necessary, 10=moribund; fatal processes progressing rapidly and 0=dead. Lower the score worse is survival for most serious illnesses. ITT population was analysed. "n"=subjects with available data for each specified category. 99999=upper

limit of 95% CI could not be estimated due to less number of subjects with event.

End point type	Secondary

End point timeframe:

Baseline of B3461023, Month 42, 54, 78, 90, 102, 114, 126 and 138

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 42 (n= 37, 34)	83.8 (± 11.63)	81.5 (± 11.32)		
Month 54 (n= 36, 34)	86.1 (± 10.22)	82.1 (± 11.49)		
Month 78 (n= 9, 7)	78.9 (± 14.53)	81.4 (± 16.76)		
Month 90 (n= 9, 6)	75.6 (± 15.09)	81.7 (± 14.72)		
Month 102 (n= 7, 5)	68.6 (± 16.76)	80.0 (± 10.00)		
Month 114 (n= 4, 4)	75.0 (± 12.91)	82.5 (± 9.57)		
Month 126 (n= 2, 2)	75.0 (± 7.07)	75.0 (± 21.21)		
Month 138 (n= 1, 1)	70.0 (± 99999)	60.0 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: NonVal30Met Group: Change From B3461022 Baseline in Karnofsky Performance Scale (KPS) Score at Month 6, 24, 36, 48, 72, 84, 96, 108 and 120

End point title	NonVal30Met Group: Change From B3461022 Baseline in Karnofsky Performance Scale (KPS) Score at Month 6, 24, 36, 48, 72, 84, 96, 108 and 120[60]

End point description:

KPS:used for rating subject ADLs on 11-step scale from 0-100, higher score=subject is better able to carry out daily activities. Score range: 100=normal no complaints; no disease evidence, 90=able to carry normal activity; minor signs/symptoms of disease, 80=normal activity with effort; some signs/symptoms, 70=cares for self; unable to carry on normal activity, 60=requires occasional assistance, but able to care for most personal needs, 50=requires considerable assistance and frequent medical care, 40=disabled; requires special care, assistance, 30=severely disabled; hospital admission indicated, death not imminent, 20=very sick; hospital admission necessary, 10=moribund; fatal processes progressing rapidly and 0=dead. Lower the score worse is survival for most serious illnesses. ITT population was analysed. "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline of B3461022, Month 6, 24, 36, 48, 72, 84, 96, 108 and 120

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: units on a scale				
least squares mean (standard error)				
Change at Month 6 (n= 18)	-0.9 (± 2.57)			
Change at Month 24 (n= 18)	-5.3 (± 2.57)			
Change at Month 36 (n= 11)	-4.8 (± 3.09)			
Change at Month 48 (n= 10)	-10.6 (± 3.22)			
Change at Month 72 (n= 4)	-10.1 (± 4.76)			
Change at Month 84 (n= 2)	-3.3 (± 6.56)			
Change at Month 96 (n= 2)	-3.3 (± 6.56)			
Change at Month 108 (n= 2)	-3.3 (± 6.56)			
Change at Month 120 (n= 2)	-33.3 (± 6.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Val30Met Group: Number of Subjects by Ambulation Stage at Week 12, Month 6, 9, 12, 18, 21, 24, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 108, 111, 114, 117, 120, 123, 126, 129

End point title	Val30Met Group: Number of Subjects by Ambulation Stage at Week 12, Month 6, 9, 12, 18, 21, 24, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 108, 111, 114, 117, 120, 123, 126, 129[61]

End point description:

Ambulatory status for each Val30Met subject was collected using ambulatory data collection forms in [Fx-005 (B3461020, Fx-006 (B3461021)] or forms based on mPND score in B3461023 (after protocol amendment 1.1). The data were categorised to 3 ambulation stages: Stage 1 (normal), Stage 2 (some assistance required), or Stage 3 (not ambulatory). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Week 12, Month 6, 9, 12, 18, 21, 24, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 108, 111, 114, 117, 120, 123, 126 and 129

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: subjects				
Week 12: Stage 1 (Normal) (n=37,36)	37	36		
Week 12:Stage 2 (Some assistance req.) (n=37,36)	0	0		

Week 12: Stage 3 (Not ambulatory) (n= 37, 36)	0	0		
Month 6: Stage 1 (Normal) (n= 37, 36)	37	36		
Month 6:Stage 2 (Some assistance req.) (n= 37, 36)	0	0		
Month 6: Stage 3 (Not ambulatory) (n= 37, 36)	0	0		
Month 9: Stage 1 (Normal) (n= 37, 36)	37	36		
Month 9:Stage 2 (Some assistance req.) (n= 37, 36)	0	0		
Month 9: Stage 3 (Not ambulatory) (n= 37, 36)	0	0		
Month 12: Stage 1 (Normal) (n= 37, 36)	37	36		
Month 12:Stage 2 (Some assistance req.) (n= 37,36)	0	0		
Month 12: Stage 3 (Not ambulatory) (n= 37, 36)	0	0		
Month 18: Stage 1 (Normal) (n= 37, 36)	37	36		
Month 18:Stage 2 (Some assistance req.) (n= 37,36)	0	0		
Month 18: Stage 3 (Not ambulatory) (n= 37, 36)	0	0		
Month 21: Stage 1 (Normal) (n= 37, 36)	37	36		
Month 21:Stage 2 (Some assistance req.) (n= 37,36)	0	0		
Month 21: Stage 3 (Not ambulatory) (n= 37, 36)	0	0		
Month 24: Stage 1 (Normal) (n= 38, 36)	37	36		
Month 24:Stage 2 (Some assistance req.) (n= 38,36)	0	0		
Month 24: Stage 3 (Not ambulatory) (n= 38, 36)	1	0		
Month 33: Stage 1 (Normal) (n= 37, 35)	37	34		
Month 33:Stage 2 (Some assistance req.) (n= 37,35)	0	1		
Month 33: Stage 3 (Not ambulatory) (n= 37,35)	0	0		
Month 36: Stage 1 (Normal) (n= 37, 35)	35	34		
Month 36:Stage 2 (Some assistance req.) (n= 37,35)	2	1		
Month 36: Stage 3 (Not ambulatory) (n= 37, 35)	0	0		
Month 39: Stage 1 (Normal) (n= 37, 35)	35	34		
Month 39:Stage 2 (Some assistance req.) (n= 37,35)	2	1		
Month 39: Stage 3 (Not ambulatory) (n= 37, 35)	0	0		
Month 42: Stage 1 (Normal) (n= 37, 34)	36	33		
Month 42:Stage 2 (Some assistance req.) (n= 37,34)	1	1		
Month 42: Stage 3 (Not ambulatory) (n= 37, 34)	0	0		
Month 45: Stage 1 (Normal) (n= 37, 34)	36	33		

Month 45:Stage 2 (Some assistance req.) (n= 37,34)	1	1		
Month 45: Stage 3 (Not ambulatory) (n= 37, 34)	0	0		
Month 48: Stage 1 (Normal) (n= 36, 34)	34	32		
Month 48:Stage 2 (Some assistance req.) (n= 36,34)	2	2		
Month 48: Stage 3 (Not ambulatory) (n= 36, 34)	0	0		
Month 51: Stage 1 (Normal) (n= 36, 34)	34	31		
Month 51:Stage 2 (Some assistance req.) (n= 36,34)	2	3		
Month 51: Stage 3 (Not ambulatory) (n= 36, 34)	0	0		
Month 54: Stage 1 (Normal) (n=34, 31)	32	27		
Month 54:Stage 2 (Some assistance req.) (n=34,31)	2	4		
Month 54: Stage 3 (Not ambulatory) (n=34, 31)	0	0		
Month 57: Stage 1 (Normal) (n=34, 31)	32	27		
Month 57:Stage 2 (Some assistance req.) (n=34,31)	2	4		
Month 57: Stage 3 (Not ambulatory) (n=34, 31)	0	0		
Month 60: Stage 1 (Normal) (n=32, 31)	30	26		
Month 60:Stage 2 (Some assistance req.) (n=32,31)	2	5		
Month 60: Stage 3 (Not ambulatory) (n=32, 31)	0	0		
Month 63: Stage 1 (Normal) (n=29, 27)	27	22		
Month 63:Stage 2 (Some assistance req.) (n=29,27)	2	5		
Month 63: Stage 3 (Not ambulatory) (n=29, 27)	0	0		
Month 69: Stage 1 (Normal) (n=11, 8)	9	5		
Month 69:Stage 2 (Some assistance req.) (n=11,8)	2	3		
Month 69: Stage 3 (Not ambulatory) (n=11, 8)	0	0		
Month 72: Stage 1 (Normal) (n=9, 7)	8	5		
Month 72:Stage 2 (Some assistance req.) (n=9,7)	1	2		
Month 72: Stage 3 (Not ambulatory) (n=9, 7)	0	0		
Month 75: Stage 1 (Normal) (n=9, 6)	8	4		
Month 75:Stage 2 (Some assistance req.) (n=9,6)	1	2		
Month 75: Stage 3 (Not ambulatory) (n=9, 6)	0	0		
Month 78: Stage 1 (Normal) (n=9, 6)	8	4		
Month 78:Stage 2 (Some assistance req.) (n=9,6)	1	2		
Month 78: Stage 3 (Not ambulatory) (n=9, 6)	0	0		
Month 81: Stage 1 (Normal) (n=9, 6)	8	4		
Month 81:Stage 2 (Some assistance req.) (n=9,6)	1	2		

Month 81: Stage 3 (Not ambulatory) (n=9, 6)	0	0		
Month 84: Stage 1 (Normal) (n=9, 6)	8	4		
Month 84:Stage 2 (Some assistance req.) (n=9,6)	1	2		
Month 84: Stage 3 (Not ambulatory) (n=9, 6)	0	0		
Month 87: Stage 1 (Normal) (n=9, 6)	8	4		
Month 87:Stage 2 (Some assistance req.) (n=9,6)	1	2		
Month 87: Stage 3 (Not ambulatory) (n=9, 6)	0	0		
Month 90: Stage 1 (Normal) (n=9, 5)	7	3		
Month 90:Stage 2 (Some assistance req.) (n=9,5)	2	2		
Month 90: Stage 3 (Not ambulatory) (n=9, 5)	0	0		
Month 93: Stage 1 (Normal) (n= 7, 5)	5	3		
Month 93:Stage 2 (Some assistance req.) (n= 7,5)	2	2		
Month 93: Stage 3 (Not ambulatory) (n= 7, 5)	0	0		
Month 96: Stage 1 (Normal) (n= 7, 4)	5	3		
Month 96:Stage 2 (Some assistance req.) (n= 7,4)	1	1		
Month 96: Stage 3 (Not ambulatory) (n= 7, 4)	1	0		
Month 99: Stage 1 (Normal) (n= 5, 4)	4	3		
Month 99:Stage 2 (Some assistance req.) (n= 5,4)	1	1		
Month 99: Stage 3 (Not ambulatory) (n= 5, 4)	0	0		
Month 102: Stage 1 (Normal) (n= 4, 4)	3	3		
Month 102:Stage 2 (Some assistance req.) (n= 4,4)	1	1		
Month 102: Stage 3 (Not ambulatory) (n= 4, 4)	0	0		
Month 105: Stage 1 (Normal) (n= 4, 4)	3	3		
Month 105:Stage 2 (Some assistance req.) (n= 4,4)	1	1		
Month 105: Stage 3 (Not ambulatory) (n= 4, 4)	0	0		
Month 108: Stage 1 (Normal) (n= 3, 4)	2	3		
Month 108:Stage 2 (Some assistance req.) (n= 3,4)	1	1		
Month 108: Stage 3 (Not ambulatory) (n= 3, 4)	0	0		
Month 111: Stage 1 (Normal) (n= 2, 2)	2	1		
Month 111:Stage 2 (Some assistance req.) (n= 2, 2)	0	1		
Month 111: Stage 3 (Not ambulatory) (n= 2, 2)	0	0		
Month 114: Stage 1 (Normal) (n= 2, 2)	2	1		
Month 114:Stage 2 (Some assistance req.) (n= 2,2)	0	1		
Month 114: Stage 3 (Not ambulatory) (n= 2, 2)	0	0		
Month 117: Stage 1 (Normal) (n= 2, 2)	2	1		
Month 117:Stage 2 (Some assistance req.) (n= 2,2)	0	1		

Month 117: Stage 3 (Not ambulatory) (n= 2, 2)	0	0		
Month 120: Stage 1 (Normal) (n= 2, 2)	2	1		
Month 120:Stage 2 (Some assistance req.) (n= 2,2)	0	1		
Month 120: Stage 3 (Not ambulatory) (n= 2, 2)	0	0		
Month 123: Stage 1 (Normal) (n= 2, 2)	2	1		
Month 123:Stage 2 (Some assistance req.) (n= 2,2)	0	1		
Month 123: Stage 3 (Not ambulatory) (n= 2, 2)	0	0		
Month 126: Stage 1 (Normal) (n= 2, 2)	2	1		
Month 126:Stage 2 (Some assistance req.) (n= 2,2)	0	1		
Month 126: Stage 3 (Not ambulatory) (n= 2, 2)	0	0		
Month 129: Stage 1 (Normal) (n= 1, 1)	1	0		
Month 129:Stage 2 (Some assistance req.) (n= 1,1)	0	1		
Month 129: Stage 3 (Not ambulatory) (n= 1, 1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: NonVal30Met Group: Number of Subjects by Ambulation Stage at Month 3, 6, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 108, 111, 114, 117, 120, 123, 126, 129

End point title	NonVal30Met Group: Number of Subjects by Ambulation Stage at Month 3, 6, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 108, 111, 114, 117, 120, 123, 126, 129[62]

End point description:

Ambulatory status for each NonVal30Met subject was collected using ambulatory data collection forms in Fx1A-201 (B3461022) or forms based on mPND score in B3461023 (after protocol amendment 1.1). The data were categorised to 3 ambulation stages: Stage 1 (normal), Stage 2 (some assistance required), or Stage 3 (not ambulatory). ITT population included all enrolled subjects who had taken at least one dose of study medication, and who had baseline and at least one post-baseline NIS-LL measure. Here, "n"=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Month 3, 6, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 108, 111, 114, 117, 120, 123, 126 and 129

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports data for the reporting groups specified.

End point values	NonVal30Met: Tafamidis			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: subjects				
Month 3: Stage 1 (Normal) (n=12)	7			
Month 3:Stage 2 (Some assistance required) (n=12)	5			
Month 3: Stage 3 (Not ambulatory) (n=12)	0			
Month 6: Stage 1 (Normal) (n=12)	7			
Month 6:Stage 2 (Some assistance required) (n=12)	5			
Month 6: Stage 3 (Not ambulatory) (n=12)	0			
Month 15: Stage 1 (Normal) (n=14)	7			
Month 15:Stage 2 (Some assistance required) (n=14)	5			
Month 15: Stage 3 (Not ambulatory) (n=14)	2			
Month 18: Stage 1 (Normal) (n=15)	7			
Month 18:Stage 2 (Some assistance required) (n=15)	6			
Month 18: Stage 3 (Not ambulatory) (n=15)	2			
Month 21: Stage 1 (Normal) (n=15)	7			
Month 21:Stage 2 (Some assistance required) (n=15)	6			
Month 21: Stage 3 (Not ambulatory) (n=15)	2			
Month 24: Stage 1 (Normal) (n=16)	8			
Month 24:Stage 2 (Some assistance required) (n=16)	6			
Month 24: Stage 3 (Not ambulatory) (n=16)	2			
Month 27: Stage 1 (Normal) (n=15)	7			
Month 27:Stage 2 (Some assistance required) (n=15)	7			
Month 27: Stage 3 (Not ambulatory) (n=15)	1			
Month 30: Stage 1 (Normal) (n=13)	5			
Month 30:Stage 2 (Some assistance required) (n=13)	7			
Month 30: Stage 3 (Not ambulatory) (n=13)	1			
Month 33: Stage 1 (Normal) (n=13)	4			
Month 33:Stage 2 (Some assistance required) (n=13)	8			
Month 33: Stage 3 (Not ambulatory) (n=13)	1			
Month 36: Stage 1 (Normal) (n=13)	3			
Month 36:Stage 2 (Some assistance required) (n=13)	9			
Month 36: Stage 3 (Not ambulatory) (n=13)	1			
Month 39: Stage 1 (Normal) (n=12)	3			
Month 39:Stage 2 (Some assistance required) (n=12)	8			

Month 39: Stage 3 (Not ambulatory) (n=12)	1				
Month 42: Stage 1 (Normal) (n=10)	2				
Month 42:Stage 2 (Some assistance required) (n=10)	6				
Month 42: Stage 3 (Not ambulatory) (n=10)	2				
Month 45: Stage 1 (Normal) (n=8)	1				
Month 45:Stage 2 (Some assistance required) (n=8)	6				
Month 45: Stage 3 (Not ambulatory) (n=8)	1				
Month 48: Stage 1 (Normal) (n=7)	2				
Month 48:Stage 2 (Some assistance required) (n=7)	5				
Month 48:Stage 3 (Not ambulatory) (n=7)	0				
Month 51: Stage 1 (Normal) (n=7)	1				
Month 51:Stage 2 (Some assistance required) (n=7)	6				
Month 51:Stage 3 (Not ambulatory) (n=7)	0				
Month 54: Stage 1 (Normal) (n=7)	1				
Month 54:Stage 2 (Some assistance required) (n=7)	6				
Month 54:Stage 3 (Not ambulatory) (n=7)	0				
Month 57: Stage 1 (Normal) (n=7)	1				
Month 57:Stage 2 (Some assistance required) (n=7)	6				
Month 57:Stage 3 (Not ambulatory) (n=7)	0				
Month 63: Stage 1 (Normal) (n=4)	1				
Month 63:Stage 2 (Some assistance required) (n=4)	3				
Month 63:Stage 3 (Not ambulatory) (n=4)	0				
Month 66: Stage 1 (Normal) (n=4)	1				
Month 66:Stage 2 (Some assistance required) (n=4)	3				
Month 66:Stage 3 (Not ambulatory) (n=4)	0				
Month 69: Stage 1 (Normal) (n=3)	1				
Month 69:Stage 2 (Some assistance required) (n=3)	2				
Month 69:Stage 3 (Not ambulatory) (n=3)	0				
Month 72: Stage 1 (Normal) (n=3)	1				
Month 72:Stage 2 (Some assistance required) (n=3)	2				
Month 72:Stage 3 (Not ambulatory) (n=3)	0				
Month 75: Stage 1 (Normal) (n=2)	1				
Month 75:Stage 2 (Some assistance required) (n=2)	1				
Month 75:Stage 3 (Not ambulatory) (n=2)	0				
Month 78: Stage 1 (Normal) (n=2)	1				
Month 78:Stage 2 (Some assistance required) (n=2)	1				

Month 78:Stage 3 (Not ambulatory) (n=2)	0				
Month 81: Stage 1 (Normal) (n=2)	1				
Month 81:Stage 2 (Some assistance required) (n=2)	1				
Month 81:Stage 3 (Not ambulatory) (n=2)	0				
Month 84: Stage 1 (Normal) (n=2)	1				
Month 84:Stage 2 (Some assistance required) (n=2)	1				
Month 84:Stage 3 (Not ambulatory) (n=2)	0				
Month 87: Stage 1 (Normal) (n=2)	1				
Month 87:Stage 2 (Some assistance required) (n=2)	1				
Month 87:Stage 3 (Not ambulatory) (n=2)	0				
Month 90: Stage 1 (Normal) (n=2)	1				
Month 90:Stage 2 (Some assistance required) (n=2)	1				
Month 90: Stage 3 (Not ambulatory) (n=2)	0				
Month 93: Stage 1 (Normal) (n=2)	1				
Month 93:Stage 2 (Some assistance required) (n=2)	1				
Month 93: Stage 3 (Not ambulatory) (n=2)	0				
Month 96: Stage 1 (Normal) (n=2)	1				
Month 96:Stage 2 (Some assistance required) (n=2)	1				
Month 96: Stage 3 (Not ambulatory) (n=2)	0				
Month 99: Stage 1 (Normal) (n=2)	1				
Month 99:Stage 2 (Some assistance required) (n=2)	1				
Month 99: Stage 3 (Not ambulatory) (n=2)	0				
Month 102: Stage 1 (Normal) (n=2)	1				
Month 102:Stage 2 (Some assistance required) (n=2)	1				
Month 102: Stage 3 (Not ambulatory) (n=2)	0				
Month 105: Stage 1 (Normal) (n=2)	1				
Month 105:Stage 2 (Some assistance required) (n=2)	1				
Month 105: Stage 3 (Not ambulatory) (n=2)	0				
Month 108: Stage 1 (Normal) (n=2)	1				
Month 108:Stage 2 (Some assistance required) (n=2)	1				
Month 108: Stage 3 (Not ambulatory) (n=2)	0				
Month 111: Stage 1 (Normal) (n=2)	1				
Month 111:Stage 2 (Some assistance required) (n=2)	1				
Month 111: Stage 3 (Not ambulatory) (n=2)	0				
Month 114: Stage 1 (Normal) (n=2)	1				
Month 114:Stage 2 (Some assistance required) (n=2)	1				

Month 114: Stage 3 (Not ambulatory) (n=2)	0				
Month 117: Stage 1 (Normal) (n=2)	1				
Month 117:Stage 2 (Some assistance required) (n=2)	1				
Month 117: Stage 3 (Not ambulatory) (n=2)	0				
Month 120: Stage 1 (Normal) (n=2)	1				
Month 120:Stage 2 (Some assistance required) (n=2)	1				
Month 120: Stage 3 (Not ambulatory) (n=2)	0				
Month 123: Stage 1 (Normal) (n=2)	1				
Month 123:Stage 2 (Some assistance required) (n=2)	1				
Month 123: Stage 3 (Not ambulatory) (n=2)	0				
Month 126: Stage 1 (Normal) (n=1)	1				
Month 126:Stage 2 (Some assistance required) (n=1)	0				
Month 126: Stage 3 (Not ambulatory) (n=1)	0				
Month 129: Stage 1 (Normal) (n=1)	1				
Month 129:Stage 2 (Some assistance required) (n=1)	0				
Month 129: Stage 3 (Not ambulatory) (n=1)	0				

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious AEs

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious AEs

End point description:

An AE was any untoward medical occurrence in a subject who received investigational product without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalisation; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; medically important events. Treatment-emergent AEs were events that emerged after enrollment in B3461023 (Fx1A-303) or which worsened during the course of B3461023 (Fx1A-303) relative to the pretreatment state. AEs included both SAEs and non-SAEs. Safety population included all enrolled subjects in the current study B3461023 (Fx1A-303) and who had taken at least one dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline (i.e., Day 0 of B3461023) up to 10 years

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis	NonVal30Met: Tafamidis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	37	18	
Units: subjects				
Treatment-Emergent AEs	35	33	18	
Treatment-emergent SAEs	6	9	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormality in Physical Examinations

End point title	Number of Subjects With Abnormality in Physical Examinations

End point description:

Complete physical examination included examination of the general appearance, head and neck, ears, eyes, nose, throat, respiratory, genitourinary, endocrine, cardiovascular, abdomen, skin, musculoskeletal, neurological, immunologic/allergies, hematologic/lymphatic. Abnormality in physical findings were based on investigator's decision. Safety population included all enrolled subjects in the current study B3461023 (Fx1A-303) and who had taken at least one dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline (i.e., Day 0 of B3461023) up to 10 years

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis	NonVal30Met: Tafamidis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	37	18	
Units: subjects	29	32	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Test Abnormalities

End point title	Number of Subjects With Laboratory Test Abnormalities

End point description:

Abnormalities criteria: Serum chemistry (bilirubin>1.5*upper limit normal [ULN]; aspartate aminotransferase; alanine aminotransferase; alkaline phosphatase; gamma glutamyl transferase >3.0*ULN; albumin<0.8*lower limit normal [LLN],>1.2*ULN; blood urea nitrogen, creatinine>1.3*ULN; free T4, thyrotropin, thyroxine <0.8*LLN,>1.2*ULN; glucose<0.6*LLN,>1.5*ULN); Coagulation (prothrombin time, prothrombin int. normalized ratio >1.1*ULN); Hematology(basophils; eosinophils, monocytes >1.2*ULN; leukocytes <0.6*LLN,>1.5*ULN; lymphocytes, neutrophils <0.8*LLN, >1.2*ULN). Safety population included all enrolled subjects in the current study B3461023 (Fx1A-303) and who had taken at least one dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline (i.e., Day 0 of B3461023) up to 10 years

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis	NonVal30Met: Tafamidis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	37	18	
Units: subjects	21	21	12	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With Electrocardiogram (ECG) Abnormalities

End point description:

Twelve-lead ECGs were obtained for all subjects. Criteria for QT interval, Bazett's correction formula (QTcB) and Fridericia's correction formula (QTcF): greater than (>) 450-480 millisecond (msec), >480-500 msec and >500 msec. Findings were considered to be abnormal based on investigator's decision. Safety population included all enrolled subjects in the current study B3461023 (Fx1A-303) and who had taken at least one dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline (i.e., Day 0 of B3461023) up to 10 years

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis	NonVal30Met: Tafamidis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	37	18	
Units: subjects				
QT Interval (msec): >450-480	8	7	6	
QT Interval (msec): >480-500	3	2	4	
QT Interval (msec): >500	2	1	6	
QTcB (msec): >450-480	14	20	11	
QTcB (msec): >480-500	6	3	5	
QTcB (msec): >500	5	3	5	
QTcF (msec): >450-480	7	7	7	
QTcF (msec): >480-500	4	2	3	
QTcF (msec): >500	5	3	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes from Baseline in Vital Signs

End point title	Number of Subjects With Clinically Significant Changes from Baseline in Vital Signs

End point description:

Criteria for clinically significant changes: Supine and standing systolic blood pressure (BP): decrease from baseline of less than or equal to (<=) -20 millimeter of mercury (mmHg), increase from baseline of greater than or equal to (>=) 20 mmHg, systolic BP <90 mmHg or >180 mmHg; Supine and standing diastolic BP: decrease from baseline of <=-15 mmHg, increase from baseline of >= 15 mmHg, diastolic BP <50 mmHg or >105 mmHg; Supine and standing pulse rate: decrease from baseline of <=-15 beats per minute (bpm), increase from baseline of >=15 bpm, pulse rate <50 bpm or >120 bpm; Weight: decrease from baseline of <=-7 percentage (%) or increase from baseline of >=7%.

End point type	Secondary

End point timeframe:

From Baseline (i.e., Day 0 of B3461023) up to 10 years

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis	NonVal30Met: Tafamidis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	37	18	
Units: subjects	38	37	18	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Any Concomitant Medications Usage

End point title	Number of Subjects With Any Concomitant Medications Usage

End point description:

Number of subjects with any concomitant medications usage are reported. Safety population included all enrolled subjects in the current study B3461023 (Fx1A-303) and who had taken at least one dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline (i.e., Day 0 of B3461023) up to 10 years

End point values	Val30Met: Tafamidis Then Tafamidis	Val30Met: Placebo Then Tafamidis	NonVal30Met: Tafamidis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	37	18	
Units: subjects	36	37	17	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
From Baseline (i.e., Day 0 of B3461023) up to 10 years	

Adverse event reporting additional description:

Same event may appear as both an AE and Serious Adverse Events (SAE). However, what is presented are distinct events. An event may be categorised as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event. Analysis performed on safety set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Val30Met: Tafamidis Then Tafamidis

Reporting group description:

Val30Met subjects who received tafamidis in study Fx-005 (B3461020), continued the same in study Fx-006 (B3461021), received tafamidis 20 mg soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Reporting group title	NonVal30Met: Tafamidis

Reporting group description:

NonVal30Met subjects who received tafamidis in study Fx1A-201 (B3461022), received tafamidis 20 mg soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Reporting group title	Val30Met: Placebo Then Tafamidis

Reporting group description:

Val30Met subjects who received placebo in study Fx-005 (B3461020) and assigned to receive tafamidis in study Fx-006 (B3461021) and study B3461023 (Fx1A-303), received tafamidis 20 mg soft gelatin capsule orally once daily for up to 10 years from the date of enrollment in this study B3461023 (Fx1A-303) or until they had an access to tafamidis for ATTR-PN via prescription, upon regulatory approval in respective countries.

Serious adverse events	Val30Met: Tafamidis Then Tafamidis	NonVal30Met: Tafamidis	Val30Met: Placebo Then Tafamidis
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 38 (15.79%)	10 / 18 (55.56%)	9 / 37 (24.32%)
number of deaths (all causes)	3	7	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central Nervous System Lymphoma			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lymphoma			

subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic Hypotension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Heart Transplant			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 38 (2.63%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease Progression			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oedema Peripheral			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Amyloidosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Reproductive system and breast disorders			
Cervical Dysplasia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional State			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			

subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Limb Fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist Fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina Unstable			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac Amyloidosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Arrest			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac Failure			
subjects affected / exposed	2 / 38 (5.26%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac Failure Acute			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial Effusion			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Tachycardia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dementia Alzheimer's Type			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vomitting			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatomegaly			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders

Muscular Weakness

subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Synovial Cyst

subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations

Device Related Infection

subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocarditis

subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteomyelitis

subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urinary Tract Infection			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitamin D Deficiency			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Val30Met: Tafamidis Then Tafamidis	NonVal30Met: Tafamidis	Val30Met: Placebo Then Tafamidis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 38 (89.47%)	18 / 18 (100.00%)	32 / 37 (86.49%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	1	1	2
Orthostatic Hypotension			
subjects affected / exposed	2 / 38 (5.26%)	4 / 18 (22.22%)	1 / 37 (2.70%)
occurrences (all)	2	4	1
Peripheral Vascular Disorder			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Carpal Tunnel Decompression			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Chest Pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Early Satiety			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Exercise Tolerance Decreased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 38 (2.63%)	2 / 18 (11.11%)	4 / 37 (10.81%)
occurrences (all)	1	2	4
Gait Disturbance			
subjects affected / exposed	3 / 38 (7.89%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	3	1	1

Implant Site Pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Oedema Peripheral			
subjects affected / exposed	3 / 38 (7.89%)	4 / 18 (22.22%)	1 / 37 (2.70%)
occurrences (all)	3	4	2
Social circumstances			
Walking Disability			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	4 / 37 (10.81%)
occurrences (all)	2	0	4
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Erectile Dysfunction			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	3 / 37 (8.11%)
occurrences (all)	1	0	3
Vulvovaginal Pruritus			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 38 (7.89%)	4 / 18 (22.22%)	0 / 37 (0.00%)
occurrences (all)	3	4	0
Dysphonia			
subjects affected / exposed	0 / 38 (0.00%)	3 / 18 (16.67%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Dyspnoea			
subjects affected / exposed	2 / 38 (5.26%)	2 / 18 (11.11%)	1 / 37 (2.70%)
occurrences (all)	2	2	1
Psychiatric disorders			
Depression			

subjects affected / exposed	3 / 38 (7.89%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	5	1	0
Insomnia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 18 (5.56%)	2 / 37 (5.41%)
occurrences (all)	2	1	2
Investigations			
Blood Cholesterol Increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Haemoglobin Increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Weight Decreased			
subjects affected / exposed	2 / 38 (5.26%)	2 / 18 (11.11%)	1 / 37 (2.70%)
occurrences (all)	2	2	1
Injury, poisoning and procedural complications			
Burns Second Degree			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 38 (0.00%)	3 / 18 (16.67%)	0 / 37 (0.00%)
occurrences (all)	0	5	0
Fall			
subjects affected / exposed	0 / 38 (0.00%)	12 / 18 (66.67%)	0 / 37 (0.00%)
occurrences (all)	0	25	0
Head Injury			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Joint Injury			

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Limb Injury			
subjects affected / exposed	3 / 38 (7.89%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	5	0	0
Medication Error			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Muscle Injury			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Procedural Pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Skin Abrasion			
subjects affected / exposed	1 / 38 (2.63%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences (all)	1	2	0
Skin Laceration			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Thermal Burn			
subjects affected / exposed	6 / 38 (15.79%)	1 / 18 (5.56%)	5 / 37 (13.51%)
occurrences (all)	10	1	8
Tooth Fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Traumatic Ulcer			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Wound			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0

Atrial Fibrillation			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Bundle Branch Block Bilateral			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Cardiac Failure			
subjects affected / exposed	2 / 38 (5.26%)	2 / 18 (11.11%)	1 / 37 (2.70%)
occurrences (all)	2	2	1
Cardiomyopathy			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Mitral Valve Incompetence			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Tachycardia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Balance Disorder			
subjects affected / exposed	3 / 38 (7.89%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Burning Sensation			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Carotid Artery Stenosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	3 / 38 (7.89%)	3 / 18 (16.67%)	1 / 37 (2.70%)
occurrences (all)	3	4	1
Fine Motor Skill Dysfunction			

subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Headache			
subjects affected / exposed	4 / 38 (10.53%)	1 / 18 (5.56%)	4 / 37 (10.81%)
occurrences (all)	4	1	5
Hypoaesthesia			
subjects affected / exposed	0 / 38 (0.00%)	4 / 18 (22.22%)	4 / 37 (10.81%)
occurrences (all)	0	4	4
Memory Impairment			
subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Migraine			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Neuralgia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	2	0	3
Neuropathy Peripheral			
subjects affected / exposed	1 / 38 (2.63%)	5 / 18 (27.78%)	2 / 37 (5.41%)
occurrences (all)	2	6	2
Paraesthesia			
subjects affected / exposed	3 / 38 (7.89%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	5	0	1
Presyncope			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Syncope			
subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	3	0	1

Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	3 / 38 (7.89%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Vertigo Positional			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	1	0	2
Eye disorders			
Cataract			
subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Dry Eye			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	2 / 37 (5.41%)
occurrences (all)	0	1	3
Eye Pruritus			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Vision Blurred			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	4 / 38 (10.53%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	5	0	0
Abdominal Pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	1	0	2
Abdominal Pain Lower			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Abdominal Pain Upper			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	3	0	2
Constipation			

subjects affected / exposed	3 / 38 (7.89%)	1 / 18 (5.56%)	3 / 37 (8.11%)
occurrences (all)	4	2	3

Dental Caries
subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences (all)	0	3	0

Diarrhoea
subjects affected / exposed	2 / 38 (5.26%)	4 / 18 (22.22%)	2 / 37 (5.41%)
occurrences (all)	2	6	3

Dry Mouth
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0

Dysphagia
subjects affected / exposed	0 / 38 (0.00%)	3 / 18 (16.67%)	0 / 37 (0.00%)
occurrences (all)	0	3	0

Gastritis
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1

Gastrointestinal Disorder
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0

Gastrointestinal Motility Disorder
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0

Haemorrhoids
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0

Inguinal Hernia
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0

Nausea
subjects affected / exposed	3 / 38 (7.89%)	2 / 18 (11.11%)	1 / 37 (2.70%)
occurrences (all)	3	4	1

Odynophagia
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0

Vomitting

subjects affected / exposed	4 / 38 (10.53%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	4	1	1

Hepatobiliary disorders

Cholelithiasis

subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3

Skin and subcutaneous tissue disorders

Acne

subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0

Alopecia

subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	2	0

Blister

subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1

Decubitus Ulcer

subjects affected / exposed	1 / 38 (2.63%)	2 / 18 (11.11%)	2 / 37 (5.41%)
occurrences (all)	1	2	4

Eczema

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0

Hyperhidrosis

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	2 / 37 (5.41%)
occurrences (all)	0	1	2

Night Sweats

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0

Pruritus

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	0	1	1

Purpura

subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	2	0

Skin Lesion

subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3
Skin Ulcer			
subjects affected / exposed	3 / 38 (7.89%)	2 / 18 (11.11%)	2 / 37 (5.41%)
occurrences (all)	6	2	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Haematuria			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Nephrolithiasis			
subjects affected / exposed	1 / 38 (2.63%)	2 / 18 (11.11%)	1 / 37 (2.70%)
occurrences (all)	2	4	1
Renal Failure			
subjects affected / exposed	3 / 38 (7.89%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Urinary Retention			
subjects affected / exposed	4 / 38 (10.53%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	4	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 18 (11.11%)	2 / 37 (5.41%)
occurrences (all)	2	2	2
Arthritis			
subjects affected / exposed	2 / 38 (5.26%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	2	1	2
Back Pain			
subjects affected / exposed	5 / 38 (13.16%)	0 / 18 (0.00%)	3 / 37 (8.11%)
occurrences (all)	7	0	4
Foot Deformity			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Muscle Atrophy			

subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Muscle Spasms			
subjects affected / exposed	3 / 38 (7.89%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	3	1	0
Muscular Weakness			
subjects affected / exposed	2 / 38 (5.26%)	3 / 18 (16.67%)	3 / 37 (8.11%)
occurrences (all)	3	4	4
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Neck Pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Pain in Extremity			
subjects affected / exposed	2 / 38 (5.26%)	2 / 18 (11.11%)	5 / 37 (13.51%)
occurrences (all)	2	4	10
Tendonitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Burn Infection			
subjects affected / exposed	3 / 38 (7.89%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Cellulitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Conjunctivitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1

Diverticulitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Ear Infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	3 / 37 (8.11%)
occurrences (all)	2	0	3
Gastroenteritis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis Viral			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Infected Skin Ulcer			
subjects affected / exposed	4 / 38 (10.53%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	5	0	3
Influenza			
subjects affected / exposed	3 / 38 (7.89%)	1 / 18 (5.56%)	7 / 37 (18.92%)
occurrences (all)	3	1	10
Nasopharyngitis			
subjects affected / exposed	5 / 38 (13.16%)	0 / 18 (0.00%)	3 / 37 (8.11%)
occurrences (all)	9	0	3
Onychomycosis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	3 / 37 (8.11%)
occurrences (all)	0	2	3
Pharyngitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 18 (0.00%)	3 / 37 (8.11%)
occurrences (all)	2	0	4
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 18 (11.11%)	1 / 37 (2.70%)
occurrences (all)	1	2	1

Pneumonia Streptococcal			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Pyelonephritis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Respiratory Tract Infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Sinusitis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	1 / 37 (2.70%)
occurrences (all)	0	4	3
Skin Infection			
subjects affected / exposed	3 / 38 (7.89%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	3	0	1
Tooth Abscess			
subjects affected / exposed	1 / 38 (2.63%)	0 / 18 (0.00%)	4 / 37 (10.81%)
occurrences (all)	1	0	6
Tracheobronchitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 38 (7.89%)	3 / 18 (16.67%)	3 / 37 (8.11%)
occurrences (all)	3	4	3
Urinary Tract Infection			
subjects affected / exposed	6 / 38 (15.79%)	2 / 18 (11.11%)	6 / 37 (16.22%)
occurrences (all)	11	2	10
Vaginal Infection			
subjects affected / exposed	3 / 38 (7.89%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	6	0	2
Vulvovaginal Mycotic Infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0

Wound Infection			
subjects affected / exposed	3 / 38 (7.89%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	3	0	1

Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	1	1	1
Fluid Overload			
subjects affected / exposed	0 / 38 (0.00%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Vitamin B12 Deficiency			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Vitamin D Deficiency			
subjects affected / exposed	0 / 38 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2011	Synopsis (Section 2), Sections 5.1, 6.4, 8.10, 8.11, 10.7.5, Appendix 1: Added text relating to assessment of ambulatory status: subject ambulation determined by the Investigator at every 6-month clinic visit and during each 3-month telephone follow-up (in between clinic visits), and at the end of study visit. Synopsis (Section 2), Sections 3.4, 5.1, 8.5, 8.11, 10.6, Appendix 1: Added text relating to clinical laboratory testing that involve blood samples taken at Baseline, every 6-month clinic visit, and at the end of study visit. Section 9 (Adverse Events): Entire Section 9 updated per new procedures (Pfizer). Appendix 1 (Schedule of Events): Visit windows added.
05 June 2012	Extension of study duration to up to 10 years or until subject has access to tafamidis for ATTR-PN via prescription. Upon regulatory approval for the treatment of ATTR-PN in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor. Section 8: Adverse Event Reporting – updated to reflect most updated requirements from Pfizer.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Prior to B3461023, V30M subjects completed 18 months blinded treatment (placebo or tafamidis) in Fx-005 followed by 12 months tafamidis in Fx-006; nonV30M subjects completed 12 months tafamidis in Fx1A-201.

Notes: