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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Tafamidis meglumine

PROTOCOL NO.: B3461049 (FX-R-001-S1)

PROTOCOL TITLE:

Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS) – Optional Blood Sample Collection Sub-study.

Study Center(s):

The study was conducted at 7 centers (2 in Portugal and 1 each in Argentina, Germany, Italy, Mexico and United States).

Study Initiation Date and Primary Completion or Final Completion Dates:

Study Initiation Date (First Subject First Visit): 06 August 2014
Final Completion Date (Last Subject Last Visit): 30 April 2015

Phase of Development:

Phase Not Applicable

Study Objective(s):

The objective of this sub-study was to collect blood samples planned to assist in the development and validation of a biomarker assay for transthyretin (TTR) amyloidoses.

METHODS

Study Design:

THAOS is a longitudinal, observational survey open to all patients with transthyretin-associated amyloidoses as well as carriers with TTR variant genotypes. B3461049 (FX-R-001-S1) is a sub-study of THAOS, and documents the methodology used to collect blood samples from up to 44 subjects enrolled in THAOS specifically for the purpose of biomarker assay development and validation. There was no treatment or active drug used in this sub-study.

Potential subjects were identified using the data entered into the THAOS database, the inclusion/exclusion criteria, and willingness to provide a blood sample. All subjects who participated in this sub-study were required to provide a separate written informed consent. After a subject provided written informed consent to participate in this study, a blood sample was collected by venipuncture. This occurred during a regularly scheduled visit or occurred in a specifically scheduled visit for the blood sampling. Subjects provided a single 10 mL blood sample.

Samples will be retained until they are no longer needed for the development and validation of a biomarker assay of TTR amyloidoses.

Number of Subjects (Planned and Analyzed):

It was planned that up to 44 subjects were to be enrolled including up to 20 subjects having a confirmed substitution of methionine for valine at position 30 (Val30Met) mutation and up to 24 additional samples collected from subjects specified non-Val30Met. This could include up to 3 subjects each with confirmed substitution of glutamine for glutamic acid at position 89 (Glu89Gln), substitution of leucine for phenylalanine at position 64 (Phe64Leu), substitution of alanine for threonine at position 60 (Thr60Ala), substitution of arginine for serine at position 50 (Ser50Arg), substitution of valine for isoleucine at position 107 (Ile107Val), substitution isoleucine for valine at position 20 (Val20Ile), substitution of leucine for isoleucine at position 68 (Ile68Leu), or substitution of isoleucine for valine at position 122 (Val122Ile) mutations.

This number was empirically based on the number of samples expected to provide sufficient validation of the biomarker assay being developed.

In total, 32 subjects were enrolled in this study.

Diagnosis and Main Criteria for Inclusion and Exclusion:

The study included subjects enrolled in the THAOS longitudinal observational study who had symptomatic transthyretin amyloidosis (ATTR) disease with documented Val30Met, Glu89Gln, Phe64Leu, Thr60Ala, Ser50Arg, Ile107Val, Val20Ile, Ile68Leu, or Val122Ile mutation in the TTR protein.

Study Treatment or Study Vaccine:

No treatment was administered during this sub-study.

Efficacy, Immunogenicity, Pharmacokinetic, Pharmacodynamic, or Outcomes Research Endpoints:

No efficacy, immunogenicity, pharmacokinetic, pharmacodynamic, or outcomes research evaluations were conducted in this sub-study.

Safety Evaluations:

Other than adverse event (AE) monitoring, no safety evaluations were performed in this sub-study.

Statistical Methods:

No statistical analysis plan has been developed as there is no analysis planned in this sub-study.

RESULTS

Subject Disposition and Demography:

In total, 32 subjects were enrolled in this study across 6 countries; 12 male and 20 female. The most prevalent gene mutation across subjects was Val30Met (62.5%) with the least prevalent being Thr60Ala and Val122lle (both 3.1%). A summary of demographic characteristics including genotype by gender is included in Table 1.

Table 1. Demographics Characteristics

	All (N=32)	Male (N=12)	Female (N=20)
Age at enrollment (years)			
Mean (SD)	49.23 (14.30)	47.98 (15.05)	49.97 (14.18)
Median	52.56	51.60	52.56
Min, max	21.40, 80.68	25.22, 65.16	21.40, 80.68
Race/ethnicity[a], N (%)			
Caucasian	9 (28.1)	2 (16.7)	7 (35.0)
African-American	1 (3.1)	0 (0.0)	1 (5.0)
American Hispanic	1 (3.1)	1 (8.3)	0 (0.0)
Latino American	6 (18.8)	0 (0.0)	6 (30.0)
No response	15 (46.9)	9 (75.0)	6 (30.0)
TTR genotype, N (%)			
Val20Ile	3 (9.4)	2 (16.7)	1 (5.0)
Val30Met	20 (62.5)	10 (83.3)	10 (50.0)
Ser50Arg	5 (15.6)	0 (0.0)	5 (25.0)
Thr60Ala	1 (3.1)	0 (0.0)	1 (5.0)
Glu89Gln	2 (6.3)	0 (0.0)	2 (10.0)
Val122Ile	1 (3.1)	0 (0.0)	1 (5.0)
Clinic country, N (%)			
Argentina	5 (15.6)	1 (8.3)	4 (20.0)
Germany	3 (9.4)	2 (16.7)	1 (5.0)
Italy	2 (6.3)	0 (0.0)	2 (10.0)
Mexico	5 (15.6)	0 (0.0)	5 (25.0)
Portugal	15 (46.9)	9 (75.0)	6 (30.0)
United States	2 (6.3)	0 (0.0)	2 (10.0)

a. Race/Ethnicity options available in the THAOS Electronic data capture include: Caucasian, Afro-Caribbean, African-American, American Hispanic, Latino American, Asian, and Other
Abbreviations: ala=alanine; arg=arginine; gln=glutamine; glu=glutamic acid; ile=isoleucine; leu=leucine; met=methionine; min=minimum; max=maximum; N=number of subjects; SD=standard deviation; ser=serine; thr=threonine; THAOS=transthyretin-associated amyloidosis outcomes survey; TTR=transthyretin; val=valine.

Efficacy, Immunogenicity, Pharmacokinetic, Pharmacodynamic, or Outcomes Research Results (Not Applicable):

No efficacy, immunogenicity, pharmacokinetic, pharmacodynamic, or outcomes research evaluations were conducted in this study.

Safety Results (Not Applicable):

No safety evaluations were performed and no AEs or deaths occurred.

CONCLUSION(S):

Blood was collected from 32 subjects who had the following mutations in the TTR protein: Val30Met (20 subjects), Glu89Gln (2 subjects), Thr60Ala (1 subject), Ser50Arg (5 subjects), Val20Ile (3 subjects), and Val122Ile (1 subject). The objective of the sub-study was to

collect blood samples planned to assist in the development and validation of a biomarker assay for TTR amyloidosis. There were no AEs and no safety issues during the study. No results of the validated assay are available to date.