NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: A Transthyretin Associated Amyloidosis Outcomes Survey (THAOS) SubStudy Evaluating the Effects of Tafamidis on Disease Progression in Patients With non-Val30Met Mutations and Symptomatic Neuropathy.

Date of Abstract: 11 April 2022

Name and affiliation of the main author: Mary Bachinsky, Study Clinician, Pfizer Inc.

Keywords: ATTR-PN, Val30Met, non-Val30Met, wt TTR, THAOS

Rationale and background: Transthyretin amyloid polyneuropathy (ATTR-PN) is a rare disease resulting from the misfolding of the transthyretin protein that affects an estimated 5-10,000 but is potentially as large as 38,000 patients worldwide.[1] Tafamidis (Vyndaqel) is a novel specific stabilizer of both tetrameric wildtype (wt) transthyretin (TTR) and of amyloidogenic variants of TTR. The Marketing Authorisation Holder had a specific obligation to conduct a post-authorisation study to evaluate the effect of Vyndaqel on disease progression and its long-term safety in ATTR-PN patients with a variant not including valine replaced by methionine at position 30 (non-Val30Met).

Research question and objectives: The objective of the study was to evaluate the effect of tafamidis on disease progression and its long-term safety in non-Val30Met patients.

Study design: This study was designed as a substudy of the THAOS Registry (B3461001), to assess disease progression over approximately 12 months or more of pre-tafamidis treatment (participants were to receive standard of care according to their treating physician) with disease progression over approximately 12 months of tafamidis administration in symptomatic ATTR-PN patients with non-Val30Met mutations. Although the intent was that the pre-treatment data period would be >12 months, a minimum of 9 months was permitted.

Setting: A subset of participants enrolled in the THAOS registry.

Subjects and study size, including dropouts: Adult participants enrolled in the THAOS registry (B3461001) with non-Val30Met mutations, stage I symptomatic polyneuropathy that had approximately 12 months or more of pre-treatment data and a modified polyneuropathy disability (mPND) score <IIIa at the start of the treatment period at the time of starting tafamidis. A total of 39 participants were included in the analysis.

Variables and data sources: Motor function (Medical Research Council [MRC] scale) (total and ankle + toe); Sensory perception (pinprick, touch, vibration, position) (total and toe only); Reflexes (total and quadriceps femoris + triceps surae); Body mass index (BMI) and modified BMI (mBMI); mPND score; Norfolk Quality of Life – Diabetic Neuropathy

[1] Schmidt HH, Waddington-Cruz M, Botteman MF, et al. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. Muscle Nerve 2018;57(5)(5):829-37.

(Norfolk QOL-DN); EuroQoL – 5 Dimensions (EQ-5D); Karnofsky Performance Index. Additionally, safety reporting of adverse events and serious adverse events, and health events of interest, were described.

Results: The efficacy data presented demonstrate the effects of tafamidis in slowing a participant's overall decline in physical function and quality of life. Efficacy endpoints (MRC total score, MRC ankle+toe subscale, sensory perception toe subscale, reflexes total score, reflexes quadriceps femoris + triceps surae subscale, BMI, mBMI, Norfolk QoL, and Karnofsky Performance Index) are directionally favourable for the tafamidis treatment period versus the untreated period, demonstrating that the rate of disease progression was slower during the tafamidis treatment period. EQ-5D showed no difference for the tafamidis treatment period versus the untreated period. Consistent with the slowed decline in neurologic function and Norfolk QoL and given the relatively high EQ-5D scores at baseline along with the relative stability of mPND, large changes in EQ-5D scores would not be expected. The point estimate of the sensory perception total score favoured the untreated period; however, the toe subscale (most peripheral sensory reference) favoured the tafamidis treatment period.

A total of 9 Adverse Events (AEs) during the tafamidis treatment period were reported for 6 participants. There were 4 participant deaths (Congestive heart failure [3], Cardiac failure [1]). Non-fatal Serious Adverse Events (SAEs) (Cardiac failure congestive, Transient ischaemic attack, Sinus node dysfunction, and Anal haemorrhage) were reported for 2 participants. No AEs or SAEs were assessed as related to tafamidis.

Discussion: The data presented in this study meet the objective to provide descriptive efficacy of tafamidis treatment in non-Val30Met ATTR-PN patients. The results across multiple safety and efficacy measures comprising physical function and health related quality of life (HRQoL) consistently demonstrate a slower rate of disease progression in non-Val30Met ATTR-PN participants during the tafamidis treatment period when compared with the pre-treated period. Analysis of safety data from this study is consistent with the known safety profile for tafamidis, with no new, ongoing, or closed safety signals for tafamidis as a result of this study data.

Marketing Authorisation Holder(s):

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Names and affiliations of principal investigators:

Name, degree(s)	Title	Affiliation	Address
Mary Bachinsky, MSc	Study Clinician	Pfizer, Inc	Eastern Pt Rd Groton, CT 06340