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Effects of tafamidis treatment on transthyretin (TTR) stabilization, efficacy, and safety in Japanese patients with familial amyloid polyneuropathy (TTR-FAP) with Val30Met and non-Val30Met: A phase III, open-label study

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ABSTRACT

Introduction: The efficacy and safety of tafamidis in transthyretin (TTR) familial amyloid polyneuropathy (TTR-FAP) were evaluated in this open-label study.
Methods: Japanese TTR-FAP patients ($n = 10$; mean age 60.1 years) received tafamidis meglumine (20 mg daily; median treatment duration 713.5 days). The primary endpoint was TTR stabilization at Week 8. Secondary endpoints included Neuropathy Impairment Score-Lower Limb (NIS-LL), Norfolk QOL-DN total quality of life (TQOL), and modified body mass index (mBMI).
Results: TTR stabilization was achieved in all patients at Weeks 8 and 26, 9 out of 10 patients at Week 52, and 8 out of 10 patients at Week 78. The percentage (95% CI) of NIS-LL responders (increase from baseline in NIS-LL < 2) was 80.0% (44.4, 97.5), 60.0% (26.2, 87.8), and 40.0% (12.2, 73.8) and mean(SD) NIS-LL change from baseline was 2.1 (5.6), 3.6 (4.4), and 3.3 (4.7), at Weeks 26, 52, and 78, respectively. Mean (SD) changes from baseline in TQOL and mBMI at Weeks 26, 52, and 78 were 11.8 (20.0), 9.1 (12.5), and 10.8 (13.7) for TQOL, and 26.6 (61.9), 64.9 (80.0), and 53.7 (81.4) for mBMI, respectively. Ambulation status was preserved in 4 out of 8 patients at Week 78. Most adverse events (AEs) were mild/moderate, with no discontinuations due to AEs.
Conclusions: Tafamidis stabilized TTR, was safe and well-tolerated, and was effective over 1.5 years in slowing neurologic progression and maintaining TQOL and nutrition status in TTR-FAP.

1. Introduction

Transthyretin (TTR) familial amyloid polyneuropathy (TTR-FAP) is a rare, inherited, life-threatening amyloidosis that presents as a progressive sensorimotor and autonomic polyneuropathy with death occurring approximately within 5–10 years from initial presentation of symptoms [1,2]. Val30Met is the most common mutation associated with TTR-FAP, accounting for approximately 85% of cases worldwide [3–6]. The age at onset of TTR-FAP varies between the second and ninth decade of life, and is dependent on phenotype, genotype, and environmental factors [4,7]. For Japanese patients with the Val30Met mutation, the mean age of onset is 35 years in endemic areas [8] and around 60 years in non-endemic areas [9].

The prevalence of FAP in Japan was estimated to be 0.87–1.1 per 1 000 000 individuals (case numbers: 110.8–135.4) in 2003–2005 [2], and to date, the number of patients with TTR-FAP in Japan have been gradually increasing with improvement of diagnostic processes and advances in disease awareness that have accompanied the availability of treatment, however the prevalence still seems to be lower than Europe.

Liver transplantation is the historic standard of care for mild or moderate TTR-FAP [3,4], but is associated with high procedural risks,

Abbreviations: TTR, transthyretin; TTR-FAP, TTR familial amyloid polyneuropathy; mBMI, modified body mass index; NIS, Neuropathy Impairment Score; NIS-LL, Neuropathy Impairment Score-Lower Limb; NIS-UL, Neuropathy Impairment Score-Upper Limb; TQOL, Norfolk QOL-DN total quality of life; NSAID, nonsteroidal anti-inflammatory drug.

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potential life-threatening post-procedural complications, and there is a shortage of donors, especially in Japan. Additionally, large numbers of patients are not suitable transplant candidates because of their age and/or advanced disease status [10]. Therefore, there is a substantial unmet medical need for other beneficial therapies.

Tafamidis, a specific stabilizer of TTR that inhibits tetramer dissociation [11], is an oral, non-NSAID medicine that has emerged as the new standard of care for TTR-FAP. Tafamidis is the only disease-modifying therapy approved in Europe, Japan, and several Latin American and other Asia-Pacific countries to delay neurologic impairment in adult patients with early stage TTR-FAP [12–14]. The efficacy and safety of tafamidis over 30 months has been demonstrated in clinical trials, including a pivotal, double-blind, placebo-controlled trial and its open-label extension in patients with Val30Met TTR-FAP; and an open-label study in patients with non-Val30Met TTR-FAP (in which eight different TTR mutations were evaluated) [15–17]. Tafamidis slowed neurological progression, was generally safe and well tolerated, and was associated with a high degree of TTR stabilization in these studies.

In the pivotal study, pre-specified analyses of five measures of clinical disease progression, including Neuropathy Impairment Score for Lower Limbs (NIS-LL), small and large fiber measures of neuropathy, modified body mass index (mBMI), and Norfolk Quality of Life-Diabetic Neuropathy total score were improved in tafamidis-treated patients versus placebo-treated patients. Significant positive treatment group differences were observed in NIS-LL total score, small fiber measures, and mBMI at month 18 [15]. A 12-month open-label extension of the registration trial showed reduced rates of neuropathic progression with tafamidis that were sustained for a total of 30 months [16]. In a 12-month evaluation of tafamidis safety and efficacy in TTR-FAP patients with non-Val30Met TTR mutations [17], the efficacy observed with tafamidis in the prevention of disease progression was similar to that seen in TTR-FAP patients with Val30Met mutations [15].

This study was a multicenter, single-arm, open-label Phase III study in Japan to assess TTR stabilization and evaluate the efficacy, safety, and tolerability of tafamidis treatment in TTR-FAP patients with Val30Met and non-Val30Met mutations.

2. Methods

2.1. Study design

This study (ClinicalTrials.gov: NCT01435655) was a single arm, open-label, multicenter study aiming to determine TTR stabilization in addition to tafamidis safety and tolerability, and efficacy in TTR-FAP patients with Val30Met and non-Val30Met mutations. The study was conducted at two centers in Japan between 2011 and 2014.

Eligible patients were men and women aged 20 to 75 years with documented amyloid deposition by biopsy and Val30Met or other TTR mutation (non-Val30Met) that was associated with peripheral neuropathy and the symptomatic neuropathy with Karnofsky Performance Status ≥50.

Key exclusion criteria included the presence of primary/secondary amyloidosis; other causes of sensorimotor neuropathy; impaired renal or hepatic function; prior liver transplantation; and New York Heart Association Functional classification ≥3. The study protocol was approved by the Institutional Review Board at each site, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2. Study procedures

After screening and baseline assessments, all patients self-administered a once-daily oral dose of tafamidis meglumine 20 mg. Study visits for assessments were scheduled at screening (Days −30 and −1), baseline (Day 0), Weeks 2, 4, 8, 12, 26, 39, 52, 78, and then 26-week interval visits and the end of study.

2.3. Outcome measures

The primary efficacy outcome was TTR stabilization at Week 8, as measured using a validated immunoturbidimetric assay [11], and TTR stabilization at each follow-up visit after Week 8 (Weeks 26, 52, 78, and study completion or withdrawal before Week 78) was evaluated as a secondary endpoint.

Secondary outcome measures included changes from baseline in NIS (total score), NIS-LL and NIS-Upper Limbs (NIS-UL) scores, Summated 3/7 Nerve Tests Normal Deviate Scores (Σ7 and Σ3 NTs NDS), Norfolk Quality of Life-Diabetic Neuropathy Questionnaire (Norfolk QOL-DN) TQOL, mBMI, and ambulatory status over time. Changes from baseline in all of these measures were summarized using descriptive statistics.

The NIS scale [18,19] provides a total body single score of neuropathic deficits and subset scores for cranial nerves, muscle weakness, reflexes, and sensation. NIS scores range from 0 to 244, with a higher score indicating a greater degree of impairment. NIS assessments were performed twice at least 24 h apart within a 7-day period at baseline, Weeks 26, 52, 78, and the end of study. The averages of the two assessments at each visit were used for analysis. A subset of the NIS, the NIS-LL, was used to provide a total neuropathic deficit score for the lower limbs. The NIS-LL was calculated as the sum of subset scores including muscle weakness, reflexes, and sensation in great toe. The range of the NIS-LL total score is 0 to 88, with a higher total score indicating greater degrees of impairment (i.e. a score of 0 indicates no impairment). A patient with change from baseline in NIS-LL < 2 was categorized as a responder; change from baseline in NIS-LL ≥ 2 was categorized as a non-responder. NIS-UL (range 0 to 156) was used to provide a total neuropathic deficit score for the upper limbs and was calculated as NIS-UL = NIS − NIS-LL.

Summated scores including Σ7 NTs NDS and Σ3 NTSF NDS, which are obtained by summing multiple objective measures of nerve fiber impairment, have been used to detect disease progression in other neuropathies [20,21]. Σ7 NTs NDS assessed with nerve conduction studies (NCS), vibration detection threshold (VDT), and Heart Rate Response to Deep Breathing (HRDB), primarily measures large-fiber function. A higher score indicates worse nerve function. Σ3 NTSF NDS, which measures small-fiber function, is assessed using cooling and heat pain thresholds by QTS with Computer Assisted Sensory Examination (CASE IV) and HRDB. The potential range of Σ3 NTSF NDS is approximately −11.2 to 11.2, with a higher score demonstrating worse nerve function.

The Norfolk QOL-DN [22] is a self-administered questionnaire containing 35 items across five domains to assess the impact of neuropathy with higher scores reflecting worse quality of life. The TQOL ranges from −4 to 136. TQOL was assessed at baseline, Weeks 26, 52, 78, and the end of the study.

mBMI, calculated as the product of body mass index (BMI; kg/m^2) and serum albumin level (g/L), provides a more accurate indicator of malnutrition and gastrointestinal dysfunction than BMI and is an important measure of wasting in patients with TTR-FAP [23]. Change in mBMI from baseline was calculated at Weeks 8, 26, 52, and the end of study.

Ambulatory status (according to walking ability scale in polyneuropathy disability score) was evaluated at baseline, Weeks 26, 52, 78, and the end of study.

An echocardiography was performed for all patients at baseline, Week 52, Week 104, and end of study. Echocardiographic parameters (intra-ventricular septum diastole thickness, stroke volume) actual values and change from baseline were summarized descriptively at each visit.

2.4. Evaluation of TTR stabilization

Blood samples for determination of TTR stabilization were collected at Weeks 8, 26, 52, 78 and study completion or withdrawal before Week 78. Each blood sample was collected into a potassium edetic acid tube