Early Intervention With Tafamidis Provides Long-Term Benefit in Delaying Neurologic Progression in TTR Familial Amyloid Polyneuropathy

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INTRODUCTION

- Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, life-threatening disorder characterized by progressive polyneuropathy.[1]
- Among >100 different TTR mutations that increase the intrinsic potential of TTR protein to misfold and form insoluble amyloid fibrils, the most prevalent is the Val30Met (V30M) point mutation.[1]
- Tafamidis, an oral medication that kinetically stabilizes TTR protein, is approved to delay neurological progression associated with early-stage TTR-FAP in Europe, Latin America, and Asia.[2]
- The efficacy and safety of tafamidis was demonstrated in an 18-month, double-blind, randomized, placebo-controlled registration trial in 128 patients from Europe and Latin America with stage 1 (patient is fully ambulatory) V30M TTR-FAP.[3]
- Prespecified analyses of 5 validated 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, consistently favored tafamidis over placebo.[3]
- A post-hoc analysis of the registration trial used a repeated measures analysis of covariance of change from baseline in NIS-LL total score in the intent-to-treat population with baseline as a covariate.
  - Results showed that at month 18, there was a significant, clinically-relevant treatment group difference favoring tafamidis over placebo.[4]
- Following completion of the registration trial,[3] continuation of tafamidis treatment through a 12-month[5] and then ongoing open-label extension study allows the evaluation of long-term safety and efficacy of tafamidis in patients with V30M TTR-FAP.
- This analysis describes the trajectory of the disease progression for 71 patients with V30M TTR-FAP and a low level of baseline disease severity at treatment start (NIS-LL ≤10) who received tafamidis for up to 5.5 years.

METHODS

- **Data source** – Patients were enrolled in an ongoing, long-term, open-label study (ClinicalTrials.gov: NCT00925002) and had previously completed the 18-month, randomized, placebo-controlled registration trial[3] and a 12-month, open-label, single-treatment-arm extension study.[5]
- **Intervention** – Tafamidis 20 mg once daily, either since the start of the registration trial or since switching from placebo to tafamidis at the start of the 12-month extension study.
- **Data cut** – The cutoff point for this data analysis was January 7, 2015. Some patients had completed the ongoing open-label study earlier, at the time when tafamidis became commercially available in their country of residence.
- **Assessments** – Disease severity and the impact of tafamidis on neurological progression over time were evaluated using the NIS-LL (scale 0 [normal] to 88 [total impairment]). Adverse events (AEs) were also evaluated.
- **Definitions** – Baseline NIS-LL at treatment start (BL NIS-LL) was defined as the last measurement before the first active dose of tafamidis.
- **Analysis population** – All patients in the intent-to-treat population with a V30M mutation and a BL NIS-LL ≤10 points who were treated with tafamidis in the original trial or its extension and for whom follow-up data were available.
- **Analytic methodology** – The change from baseline in NIS-LL over time was analyzed descriptively.
- **Limitations** – This analysis did not include a comparator group.

RESULTS

- A total of 71 patients met the criteria for evaluation. Their baseline demographics are summarized in **Table 1**.

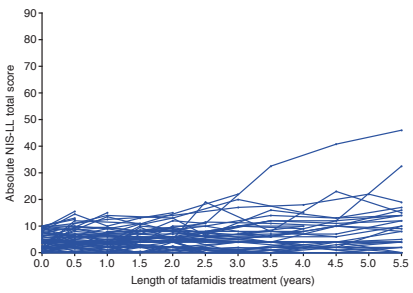
Table 1. Baseline demographics and characteristics in the population of patients with BL NIS-LL ≤10 at the start of tafamidis treatment

	BL NIS-LL ≤10 at treatment start (n=71)
Gender, n (%) females	41 (57.7)
Race, n (%)	
Caucasian	65 (91.5)
Latino American	4 (5.6)
Not available	2 (2.8)
Age at symptom onset, years	
Mean (SD)	35.7 (11.3)
Median (range)	32.0 (22–65)
Symptom duration, months	
Mean (SD)	37.6 (46.7)
Median (range)	18.2 (2–268)
mBMI, kg/m^2 × g/L	
Mean (SD)	1063 (181)
Median (range)	1066 (716–1581)
BL NIS-LL	
Mean (SD)	4.1 (3.1)
Median (range)	4.0 (0.0–10.0)

SD, standard deviation.

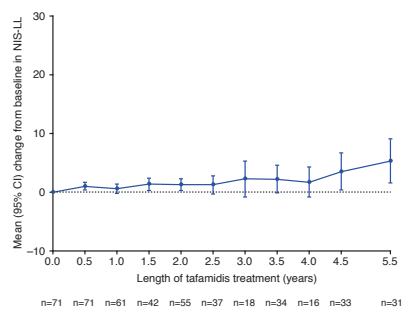
- A BL NIS-LL ≤10 at treatment start was associated with a minimal level of disease progression over time (**Figure 1**).

Figure 1. Change in NIS-LL over time for each of the 71 patients with BL NIS-LL ≤10 at the start of tafamidis treatment



- For 3 patients, the NIS-LL score increased to ≥30 points after more than 3 years of treatment (**Figure 1**).
- The mean (95% CI) change from baseline in NIS-LL was 0.6 (–0.2, 1.4) at 1 year, 1.3 (0.3, 2.3) at 2 years, 2.2 (–0.1, 4.6) at 3.5 years, 3.5 (0.4, 6.7) at 4.5 years, and 5.3 (1.6, 9.1) points after 5.5 years of tafamidis treatment (**Figure 2**).

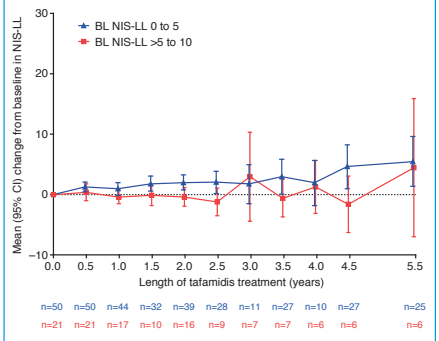
Figure 2. Mean (95% CI) change from baseline in NIS-LL for the patients with BL NIS-LL ≤10 at the start of tafamidis treatment



Year 5 data were excluded due to limited data (n=2).
CI, confidence interval.

- Additional categorization of patients by their baseline NIS-LL scores as either 0 to 5 (n=50) or >5 to 10 (n=21) at the start of treatment revealed similar disease trajectories (**Figure 3**).

Figure 3. Subgroup analysis: mean (95% CI) change from baseline in NIS-LL for patients with a BL NIS-LL score of 0 to 5 (n=50) and of >5 to 10 (n=21) at the start of tafamidis treatment



Year 5 data were excluded due to limited data (n=2).

- To put these data into further context:
  - The monthly rate of change in NIS-LL during the initial 18 months of placebo treatment in the registration trial was 0.34 points/month in the subpopulation of patients who switched from placebo to tafamidis after completing that trial (n=33),[5] corresponding to a yearly increase of approximately 4 points.
- No new safety issues or AEs of tafamidis were identified. During the 5.5 years, 3/71 patients (4%) discontinued treatment due to all-causality treatment-emergent AEs (1 diarrhea, 1 urticaria, 1 renal impairment) and 1 patient died of lymphoma 10 days after the last dose of tafamidis (the lymphoma was not considered treatment-related).

CONCLUSIONS

- A minimal level of disease progression occurred in patients with V30M TTR-FAP and low baseline disease severity, defined as NIS-LL total score ≤10 at treatment start, during long-term (5.5 years) tafamidis treatment.
- This analysis with tafamidis represents the longest longitudinal analysis of an approved oral treatment for TTR-FAP to date.
- Early intervention with tafamidis provides long-term benefit in delaying neurological progression associated with TTR-FAP and is accompanied by a favorable long-term side-effect profile.
- These data are consistent with the concept that tafamidis treatment should be initiated as early as possible in patients with symptomatic TTR-FAP.

REFERENCES

1. Ando Y, et al. *Orphanet J Rare Dis* 2013;8:31.
2. Scott LJ. *Drugs* 2014;74:1371-8.
3. Coelho T, et al. *Neurology* 2012;79:785-92.
4. Keohane D, et al. Poster presentation at the First Congress of the European Academy of Neurology (EAN); June 20-23, 2015, Berlin, Germany.
5. Coelho T, et al. *J Neurol* 2013;260:2802-14.

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CONFLICTS OF INTEREST

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