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Tafamidis Delays Disease Progression in TTR Familial Amyloid Polyneuropathy: Supportive Analyses From a Pivotal Trial

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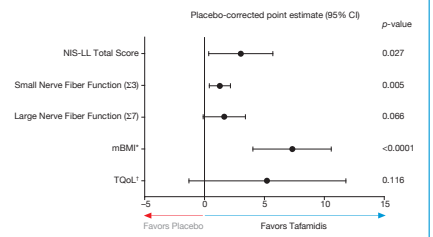
INTRODUCTION

- Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, life-threatening multisystem disease characterized by progressive polyneuropathy.
- TTR-FAP is caused by mutations in the TTR gene that increase the propensity of TTR protein to cumulatively deposit as amyloid fibrils in nerve tissues and other organs.
- The most common amyloidogenic TTR mutation worldwide is the V30M point mutation.
- Tafamidis, a TTR kinetic stabilizer and oral medication, is the first disease-modifying pharmacotherapy approved for use in adult patients with early-stage TTR-FAP in Europe, Japan, Argentina, and Mexico.[1]
- Previously, the efficacy and safety of tafamidis was demonstrated in an 18-month, double-blind, placebo-controlled study in 128 patients with early symptomatic TTR-FAP due to V30M mutations.[2]
  - Tafamidis was well tolerated and effectively stabilized TTR tetramers in 98% of recipients, with 0% TTR stabilization in the placebo group.[2]
  - Clinical outcomes for a host of prespecified, validated, clinically-accepted measures of disease progression favored tafamidis (**Figure 1**).

Figure 1. LS means treatment group differences in changes from baseline to month 18 in prespecified efficacy outcomes as estimated by the previously published repeated measures ANOVA[2]



*As mBMI deteriorates in the opposite direction than the other items, absolute mBMI values were used and the point estimate and associated 95% CI were divided by 10 to fit them onto the same scale as the other data.
†The analysis model included baseline TQoL as a covariate. For patients with post-baseline assessments, missing values at month 18 were imputed using a last observation carried forward method.
Σ3, summated 3 nerve tests small-fiber normal deviates; Σ7, summated 7 nerve tests normal deviates; ANOVA, analysis of variance; CI, confidence interval; LS, least square; mBMI, modified body mass index; NIS-LL, Neuropathy Impairment Score – Lower Limbs; TQoL, Norfolk Quality of Life-Diabetic Neuropathy total score.

- Efficacy was maintained in a subsequent 12-month open-label extension study.[3]
- Additional post-hoc analyses from the pivotal placebo-controlled trial, reported here, sought to confirm the beneficial effects of tafamidis in delaying neurologic impairment in TTR-FAP.

METHODS

- **Study population** – A total of 128 adult patients with early-stage V30M TTR-FAP from Europe (82%) and Latin America (18%).
- **Intervention** – Oral administration of tafamidis (20 mg) or placebo once daily for 18 months.
- **Outcome measures** – Disease progression was assessed by 5 validated, clinically accepted and prespecified measures: NIS-LL; Σ3; Σ7; TQoL; and mBMI (BMI multiplied by serum albumin concentration), as well as the composites, NIS-LL+Σ3 and NIS-LL+Σ7, which were added post hoc.
- **Analysis population** – All presented analyses were conducted in the intent-to-treat (ITT) population and, if not otherwise indicated, only observed data were included.
- **Repeated measures ANOVA**
  - A prespecified mixed-effects model with an unstructured covariance matrix, fixed effects for treatment, month, treatment-by-month interaction, and patient as a random effect, was used to analyze change from baseline at months 6, 12, or 18.
  - The prespecified repeated measures ANOVA of change from baseline in NIS-LL total score presented in **Figure 1** was also repeated post hoc with the addition of (1) the baseline value as a covariate or (2) sensitivity analysis using multiple imputations for missing data based on assigned treatment group (3 batches of 1000 multiply-imputed data sets).
- **Multivariate permutation analysis**
  - Post-hoc re-randomization test to determine the probability of obtaining the observed overall outcome due to chance.
  - The test statistic was the treatment group difference in mean summated rank score for change from baseline at month 18 in NIS-LL, Σ3, Σ7, TQoL, and mBMI in patients with available data for all 5 efficacy endpoints (tafamidis, n=48; placebo, n=44).
  - The null distribution of this test statistic was established by randomly assigning 48 of the observed data points to tafamidis and 44 to placebo and calculating the test statistic on each of 200,000 re-randomized data sets.

RESULTS

- Baseline characteristics of the ITT population are shown in **Table 1**.

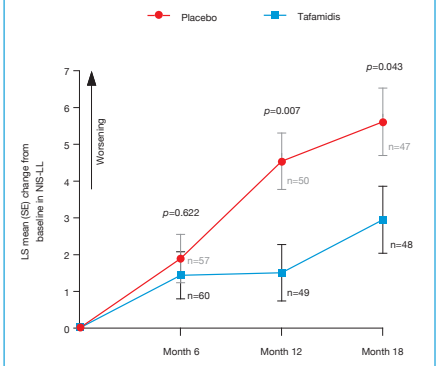
Table 1. Baseline characteristics in the ITT population[2]

Characteristic, mean (SD) or n (%)	Tafamidis n=64	Placebo n=61
Age, years	39.8 (12.7)	38.4 (12.9)
Gender, % female	32 (50%)	35 (57.4%)
mBMI, kg/m² × g/L	1005 (165)	1012 (213)
NIS-LL Total Score (scale 0 [normal] to 88 [total impairment])	8.4 (11.4)	11.4 (13.5)
TQoL Score (scale –2 [best QoL] to 138 [worst QoL])	27.3 (24.2)	30.8 (26.7)

SD, standard deviation; QoL, quality of life.

- When adjusted for baseline NIS-LL disease severity, a significant treatment group difference in change from baseline to month 18 in NIS-LL was retained (LS mean difference, 2.7 points; 95% CI, 0.1–5.2; $p<0.05$; **Figure 2**).

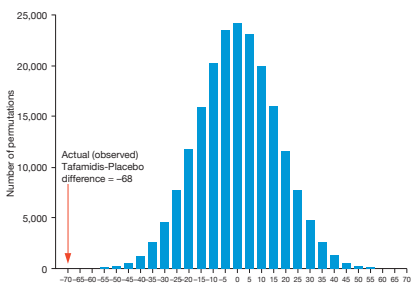
Figure 2. Post-hoc, observed case, repeated measures ANOVA with baseline as covariate assessing the treatment group difference in change from baseline in NIS-LL total score



p-values relate to the difference between treatment groups at each time point.
SE, standard error.

- The actual change from baseline in NIS-LL during the 18-month study was minimal in tafamidis recipients (LS mean, 2.9; 95% CI, 1.1–4.8) and nearly halved compared with placebo (LS mean, 5.6; 95% CI, 3.8–7.4).
- By multiple imputation analysis, worsening in mean NIS-LL scores was significantly reduced in the tafamidis group relative to placebo (treatment group LS mean difference, 2.8 points; 95% CI, 0.2–5.4; $p<0.05$).
- Significant treatment group differences in change from baseline in NIS-LL+Σ3 and NIS-LL+Σ7 favored tafamidis (**Figure 3**).
- Multivariate analysis of NIS-LL, TQoL, mBMI, Σ3, and Σ7 using a permutation approach showed that the chance of observing the current results would be 1 in 50,000 if there were no treatment effect (**Figure 4**).

Figure 4. Post-hoc global permutation analysis comparing the observed treatment group difference in sum of ranks for the 5 outcome measures at month 18 with the null distribution



Each bar represents a summed rank score range of 5 (e.g., 0 reflects permutations falling between –2.5 and +2.5).

CONCLUSIONS

- These additional prespecified and post-hoc analyses based on a placebo-controlled 18-month trial in a large sample (considering the rare nature of the disease) of patients with early-stage TTR-FAP due to the most common TTR mutation further support the beneficial effects of tafamidis in slowing deterioration of neurological function in TTR-FAP.
- TTR protein was stabilized in the majority of tafamidis recipients (98%), and this stabilization was associated with directionally consistent, clinically relevant slowing of neurological disease progression and improved QoL and nutritional status relative to placebo.
- In tafamidis recipients, change from baseline at 12 and 18 months in neurological disease progression as assessed by NIS-LL was minimal and significantly reduced compared with placebo, irrespective of statistical methodology.
- Post-hoc multivariate analysis of NIS-LL, TQoL, mBMI, Σ3, and Σ7 and analyses of neurological composite outcome measures over time provide further evidence for the clinical efficacy of tafamidis.
- Taken together, these data underscore that tafamidis clinically and significantly delayed disease progression and support the use of tafamidis for the treatment of TTR-FAP.

REFERENCES

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2. Coelho T, et al. *Neurology* 2012;79:785-92.
3. Coelho T, et al. *J Neurol* 2013;260:2802-14.

ACKNOWLEDGMENTS

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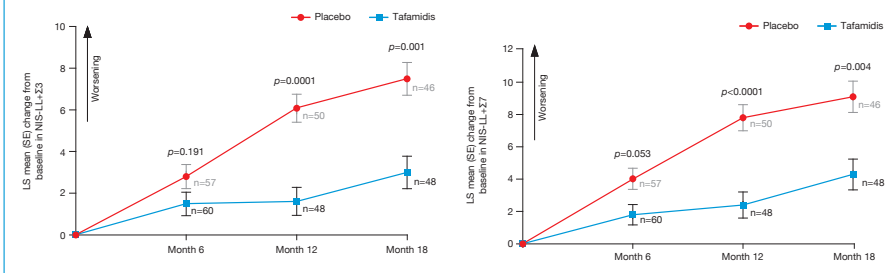
CONFLICTS OF INTEREST

DK, JS, MS, and LA are employees of Pfizer. BG is an employee of inVentiv Health Inc who provided statistical support, which was funded by Pfizer.

Figure 3. Post-hoc, observed case, repeated measures ANOVA of change from baseline in the neurophysiological composite outcome measures, NIS-LL+Σ3 and NIS-LL+Σ7



Mean (SD) NIS-LL+Σ3 [NIS-LL+Σ7] baseline scores were 13.9 (14.2) [16.1 (18.3)] for tafamidis and 17.1 (15.7) [20.2 (19.8)] for placebo.
p-values relate to the difference between treatment groups at each time point.

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