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ORIGINAL RESEARCH

Evaluation of Mortality During Long-Term Treatment with Tafamidis for Transthyretin Amyloidosis with Polyneuropathy: Clinical Trial Results up to 8.5 Years

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ABSTRACT

Introduction: The effects of tafamidis on mortality in Val30Met and non-Val30Met patients with transthyretin amyloidosis with polyneuropathy (ATTR-PN) were evaluated.

Methods: The analyses were based on cumulative data from the Val30Met patients in the 18-month double-blind registration study and its 12-month open-label extension study, the non-Val30Met patients of the 12-month open-label study, and both patient groups in the ongoing 10-year extension study. Kaplan–Meier analyses of time to death from first treatment dose were performed. For the Val30Met group, two treatment groups were analyzed: those who received tafamidis in both the parent and extension studies (T–T) and those who received placebo in the parent study and switched to tafamidis in the extension studies (P–T).

Results: Kaplan–Meier estimates (95% confidence interval [CI]) were available up to 9 years for the Val30Met group, at which time 85.9% (53.1–96.4) and 91.1% (77.9–96.6) of the patients in the T–T and P–T groups, respectively, were alive. For the non-Val30Met group, estimates were available up to 8 years from the first dose, and the percentage of patients alive was 75.9% (47.7–90.2).

Conclusion: Long-term tafamidis treatment may confer survival benefit in patients with ATTR-PN.

Trial registration: ClinicalTrials.gov identifier: NCT00409175, NCT00791492, NCT00630864, and NCT00925002.

Keywords: Amyloidosis; Mortality; Polyneuropathy; Tafamidis; Transthyretin; Val30Met

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Key Summary Points

Why carry out this study?

Tafamidis has been shown to be effective in delaying disease progression among patients with transthyretin amyloidosis with polyneuropathy (ATTR-PN), but very little is known on whether it impacts mortality.

This report represents the first evaluation of the effect of tafamidis on mortality in Val30Met and non-Val30Met patients with ATTR-PN that uses data from clinical trials where patients received up to 8.5 years of treatment.

What was learned from the study?

Over the course of 8–9 years, there were very few deaths among patients with ATTR-PN treated with tafamidis.

This finding is potentially significant given the severely shortened life span of patients with ATTR-PN and suggests that tafamidis may confer a survival benefit.

Notwithstanding study limitations, the current analysis offers an important evaluation of patients treated with tafamidis in clinical trials.

INTRODUCTION

Transthyretin amyloidosis with polyneuropathy (ATTR-PN) is a rare and fatal systemic disorder caused by mutations of the *TTR* gene that can result in damaging amyloid accumulation in peripheral nervous tissue and organs, including the heart [1]. Without treatment, disease progression is relentless and ultimately fatal, with organ failure, cachexia, sudden death, and secondary infection as common causes of death [2, 3].

The clinical progression and life expectancy of patients with ATTR-PN can vary depending on genotype, geographic origin, and age of onset [4]. Nearly 150 mutations of the *TTR* gene have been identified, with Val30Met (p.Val50Met) the most prevalently linked to ATTR-PN [4–6]. Estimates of median survival time from symptom onset in Val30Met patients can vary between 7 and 17 years, with differences largely attributed to age of onset and geographic origin (early-onset patients of Portuguese origin showing the longest median survival) [7–10]. The median survival estimates for non-Val30Met patients from symptom onset range from approximately 4 to 13 years, largely owing to genetic and phenotypic heterogeneity [8, 9, 11]. Liver transplantation, a treatment option that removes the primary source of mutated TTR, can stabilize disease progression and improve survival in carefully selected patients, primarily those with a Val30Met mutation and early onset of illness ($\leq$ 50 years of age; late-onset: $>$ 50 years) [12]. However, liver transplantation is not readily accessible in all geographical regions, requires lifelong immunosuppressive therapy, and does not eliminate continued amyloid deposition of wild-type TTR where no mutation is present in the gene [4, 13]. In addition, the survival benefit with liver transplantation is generally poorer in patients with non-Val30Met mutations (relative to early-onset Val30Met patients), although large differences in outcomes among various mutations have been described [12, 14].

Tafamidis meglumine, a selective TTR stabilizer taken orally once daily, is approved to treat ATTR-PN and is available in countries within Europe, Asia, and Latin America [15, 16]. Tafamidis has demonstrated efficacy and safety in an 18-month pivotal trial of early-onset Val30Met patients [17] and in a 12-month open-label study of non-Val30Met patients [18], with continued effects in delaying neurologic disease progression over longer-term use in open-label extension studies [19–21].

No clinical studies have been conducted to look specifically at mortality as an outcome in the ATTR-PN population, although observational data have demonstrated a survival benefit for tafamidis relative to natural disease progression and liver transplant among early-onset Val30Met patients [10]. This report represents

the first evaluation of the effect of tafamidis on mortality in Val30Met and non-Val30Met patients with ATTR-PN while receiving up to 8.5 years of treatment in clinical trials.

METHODS

Study Design and Patients

The analyses are based on cumulative data from the Val30Met patients in the original 18-month double-blind registration study and its 12-month open-label extension study [17, 19], and from the non-Val30Met patients in the 12-month open-label study [18]; eligible patients from these studies were then enrolled in an ongoing 10-year open-label extension study initiated in August 2009 (ClinicalTrials.gov identifier NCT00925002) [21].

Details on study design, protocol, eligibility criteria, and outcome measures for each study are reported elsewhere [17–19, 21]. Per the protocols, deaths are reported as part of safety monitoring during the studies and for up to 30 days after study discontinuation.

In the ongoing 10-year extension study, patients continue with once-daily oral administration of 20 mg tafamidis meglumine (soft gelatin capsule) for up to 10 years or until they have access to tafamidis through a prescription in their respective country following regulatory approval. Study centers are located in Argentina, Brazil, France, Germany, Italy, Portugal, Sweden, and the USA. The study protocol was approved by local institutional review boards and is in compliance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent. Further details of this ongoing study, including the progression of patients through the parent and extension studies and the names of institutional review boards or independent ethics committees, are available elsewhere [21, 22].

Table 1 Patient disposition in the ongoing 10-year open-label extension study

	Val30Met		Non-Val30Met Tafamidis (n = 18)
	Tafamidis-to-tafamidis[a] (n = 38)	Placebo-to-tafamidis[b] (n = 37)	
Study completion			
Yes	31 (81.6%)	27 (73.0%)	7 (38.9%)
No	5 (13.2%)	8 (21.6%)	9 (50.0%)
Ongoing	2 (5.3%)	2 (5.4%)	2 (11.1%)
Primary reason for discontinuation			
Adverse event	2 (5.3%)	1 (2.7%)	2 (11.1%)
Patient withdrew consent	1 (2.6%)	3 (8.1%)	3 (16.7%)
Liver transplant	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient died	2 (5.3%)	1 (2.7%)	4 (22.2%)
Other	0 (0.0%)	3 (8.1%)	0 (0.0%)

[a] Tafamidis-to-tafamidis refers to patients randomized to tafamidis in the registration trial and continued with tafamidis treatment in the open-label extension studies

[b] Placebo-to-tafamidis refers to patients randomized to placebo in the registration trial and switched to tafamidis in the open-label extension studies

The study is ongoing, and the cut-off date for this analysis was January 3, 2017

Statistical Analysis

Kaplan–Meier analyses of time to death in patients treated with study medication in tafamidis clinical trials were conducted with a cut-off date of January 3, 2017.

The data were analyzed for the full safety population, defined as all patients who initially enrolled in the parent studies and who received at least one dose of study medication.

The analyses were stratified by TTR mutation (Val30Met and non-Val30Met). The Val30Met group comprised the 128 patients who initiated the 18-month double-blind randomized registration trial. Data are presented by treatment: for the Val30Met group, those who received tafamidis in both the parent and extension

Table 2 Demographic and baseline characteristics in the full safety population

Characteristics	Val30Met		Non-Val30Met
	Tafamidis-to-tafamidis[a] (*n* = 65)	Placebo-to-tafamidis[b] (*n* = 63)	Tafamidis (*n* = 21)
Gender, *n* (%)			
Female	33 (50.8)	37 (58.7)	8 (38.1)
Male	32 (49.2)	26 (41.3)	13 (61.9)
Race, *n* (%)			
Caucasian	57 (87.7)	55 (87.3)	19 (90.5)
Latin American	6 (9.2)	7 (11.1)	
Asian			1 (4.8)
African–Caribbean			1 (4.8)
Not available	2 (3.1)	1 (1.6)	
Age, years			
Mean (SD)	40.0 (12.7)	38.1 (12.8)	63.1 (9.9)
Median (range)	36.0 (25–74)	34.0 (22–71)	64.3 (44–77)
mBMI, mean (SD), [g/L] × [kg/m^2]	1006.4 (164.5)	1010.7 (211.1)	1052.5 (206.7)
Symptom duration, mean (SD), years	3.9 (4.0)	2.9 (2.7)	5.4 (5.1)
NIS-LL (range, 0–88), mean (SD)	8.4 (11.3)	11.1 (13.4)	27.6 (24.7)
Norfolk QOL-DN (TQOL) (range, −2 to 138), mean (SD)	27.4 (24.0)	30.5 (26.7)	47.8 (35.1)

[a] Tafamidis-to-tafamidis refers to patients randomized to tafamidis in the registration trial and continued with tafamidis treatment in the open-label extension studies

[b] Placebo-to-tafamidis refers to patients randomized to placebo in the registration trial and switched to tafamidis in the open-label extension studies

Baseline refers to the baseline of the parent studies [17, 18]

mBMI modified body mass index, *NIS-LL* Neuropathy Impairment Score for the Lower Limbs, *Norfolk QOL-DN* Norfolk Quality of Life-Diabetic Neuropathy questionnaire, *TQOL* total quality-of-life score

studies (tafamidis-to-tafamidis, T–T, *n* = 65), and those who received placebo in the 18-month parent study and then switched to tafamidis in the extension studies (placebo-to-tafamidis, P–T, *n* = 63) [17, 19, 21]. Patients who were randomized to placebo and discontinued participation early were included in the P–T group, and patients who were randomized to tafamidis and discontinued participation early were included in the T–T group. The non-Val30Met group comprised the 21 patients who originated in the 12-month open-label study [18]. Patients were distributed across eight different genotypes.

Kaplan–Meier analyses of time to death from first dose of treatment (in the parent study) were performed. The percentage of clinical trial patients alive at yearly time intervals following the first dose of treatment was estimated. Patients who completed or discontinued study participation were censored at the last telephone contact (last visit date plus 30 days);

Table 3 Description of patient deaths across studies

Study	Patient	Genotype/ treatment	Cause of death	Relationship to study drug
18-month double-blind study in Val30Met patients	54-year-old female	Val30Met/ tafamidis	Cardiac tamponade	Unrelated
	41-year-old female	Val30Met/placebo	Hepatic failure	Unrelated
	63-year-old female	Val30Met/placebo	Sepsis	Unrelated
	35-year-old female	Val30Met/placebo	Unknown cause	Unrelated
10-year open-label extension study	66-year-old male	Val30Met/T–T	Cardiac failure	Unrelated
	72-year-old male	Val30Met/T–T	Lymphoma[a]	Unrelated
	71-year-old male	Val30Met/P–T	Ileus	Unrelated
	72-year-old female	Non-Val30Met/ tafamidis	Cardiac arrest	Unrelated
	76-year-old female	Non-Val30Met/ tafamidis	Sepsis	Unrelated
	61-year-old male	Non-Val30Met/ tafamidis	Complications following heart transplant	Unrelated
	76-year-old female	Non-Val30Met/ tafamidis	Amyloidosis	Unrelated

Two patients, who died several months after study withdrawal (one reported in Coelho et al. 2012 [17] and one reported in Barroso et al. 2017 [21]), were censored at last visit date + 30 days, per censoring rule, and are therefore not described here
P–T patients randomized to placebo in the registration trial and switched to tafamidis in the open-label extension studies (the placebo-to-tafamidis group), *T–T* patients randomized to tafamidis in the registration trial and continued with tafamidis treatment in the open-label extension studies (the tafamidis-to-tafamidis group)
[a] The patient discontinued participation in the study due to reoccurrence of pre-existing malignant lymphoma, not related to amyloidosis disease progression

ongoing patients were censored at the cut-off date of the analysis—January 3, 2017. These analyses included deaths following transplantation (liver and/or heart) or post-discontinuation collected as part of the protocol requirement for assessing adverse events through the follow-up contact 30 days after the last dose of study medication.

RESULTS

Patient Population and Baseline Characteristics

Details concerning patient disposition for the parent and extension studies were summarized previously [21]. For the ongoing 10-year extension study, patient disposition at the time of the

data cut-off for this analysis is provided in Table 1. Patients have been followed for up to 8.5 years, with some patients receiving tafamidis continuously throughout this period. The median cumulative tafamidis exposure was 4.8, 3.7, and 3.5 years for the three treatment groups Val30Met T–T (n = 64), Val30Met P–T (n = 41), and non-Val30Met (n = 21), respectively.

Demographic and baseline clinical characteristics of the full safety populations at the start of the parent studies [17, 18] are shown in Table 2. Non-Val30Met patients were older than the Val30Met patients, had a longer duration of symptoms, and showed more advanced disease in neurologic function and health-related quality of life at the initiation of the parent study.

A total of 68 patients discontinued participation in the clinical studies; the most common reason was liver and/or heart transplant. In total, 35 patients (Val30Met, n = 33; non-Val30Met, n = 2) had liver transplants, one patient (non-Val30Met) had a heart transplant, and one patient (non-Val30Met) had a combined liver/heart transplant. Patients on transplant waitlists were allowed to enroll in the tafamidis trials and discontinue participation in order to undergo the procedure when an organ became available; transplantation was not used as rescue therapy in these studies.

Patient Deaths

Descriptions of patient deaths in the parent and extension studies, including the present ongoing study, have been published [17–19, 21] and are summarized in Table 3. There have been no additional patient deaths since the previous interim analysis of the 10-year open-label extension study [21].

There were four deaths reported in the 18-month double-blind study in Val30Met patients (tafamidis, n = 1; placebo, n = 3), with each occurring following liver transplantation (Table 3) [17]. One patient, treated with tafamidis before liver transplant, died due to cardiac tamponade (complication following pacemaker insertion). Three patients treated with placebo before liver transplant died, one due to hepatic failure post-transplant, one due to sepsis post-transplant, and one from unknown cause (Table 3). None of these deaths were considered related to study treatment. One additional death occurred 3 months after the patient completed the study (due to liver transplant complications) [17] and was not included in the clinical database; therefore, this patient was not included in Table 3 or the Kaplan–Meier analysis.

No deaths were reported during the 12-month open-label extension study [19] and no deaths were reported in the 12-month open-label study in non-Val30Met patients [18].

As of the cut-off date for this analysis, seven patients (Val30Met, n = 3; non-Val30Met, n = 4) died during or within 30 days of discontinuation/completion of the ongoing extension study [21] (Table 3). None of the seven deaths were considered treatment-related.

Mortality Analysis

Kaplan–Meier curves estimating the percentage of patients alive at yearly intervals following the first dose of treatment in the parent study are shown in Fig. 1a and b for the Val30Met and non-Val30Met patients, respectively. These analyses included all 11 deaths through the follow-up contact 30 days after the last dose of study medication. The number of patients in the study decreases at later time points as patients have completed the study because of the commercial availability of drug supply. Estimates (95% confidence interval [CI]) were available up to 9 years for the Val30Met group, at which time 85.9% (53.1–96.4) and 91.1% (77.9–96.6) of the patients in the T–T and P–T treatment groups, respectively, were alive (Fig. 1a). Although formal statistical comparisons between the two treatment groups were not conducted, the large overlap between the 95% CIs indicates that the difference between them is unlikely to be statistically significant. For the non-Val30Met group, estimates were available up to 8 years from the first dose of treatment, and the percentage of patients alive was 75.9% (95% CI 47.7–90.2) (Fig. 1b).

DISCUSSION

This is the first evaluation of mortality in patients with ATTR-PN receiving long-term

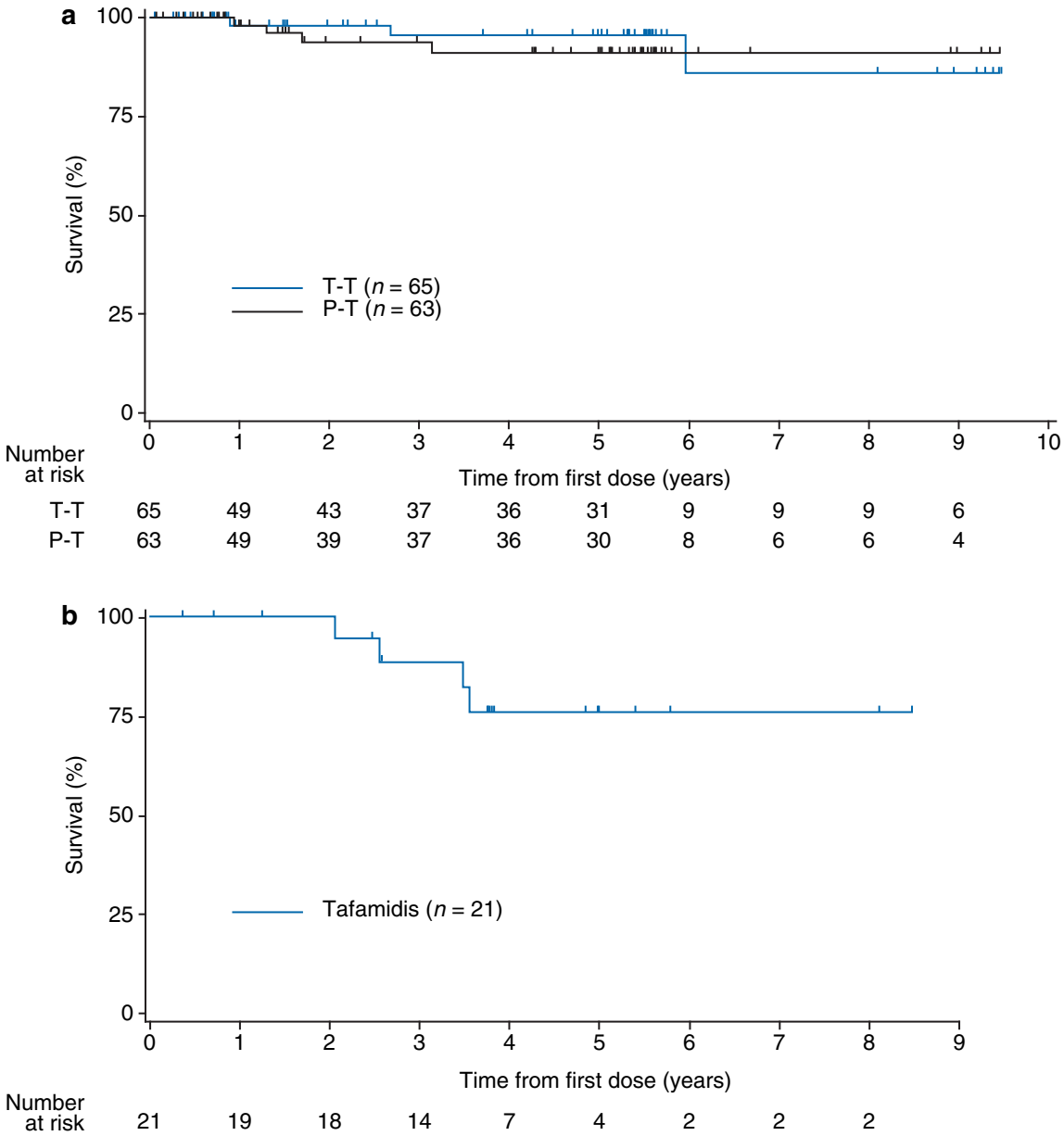

Fig. 1 Kaplan–Meier curves of patient survival while on study medication from first dose of treatment for Val30Met (**a**) and non-Val30Met (**b**) patients (full safety population, $N = 128$ and $N = 21$, respectively). Patients were censored at the last telephone contact (last visit date + 30 days) for those who concluded the study (completed or discontinued participation in the study) or at the cut-off of January 3, 2017, for ongoing patients. Val30Met patients from the parent study who were randomized to placebo and discontinued participation in that study were included in the P–T treatment, while those randomized to tafamidis and discontinued were included in the T–T treatment group. P–T, placebo treatment in the parent study followed by tafamidis treatment in the open-label extension studies ($n = 63$); T–T, tafamidis treatment in both the parent and open-label extension studies ($n = 65$)

treatment with tafamidis through prospective interventional clinical trials. Based on Kaplan–Meier analyses, approximately 85% of patients in the Val30Met group (in both the T–T and P–T treatment groups) and 75% of patients in the non-Val30Met group were alive at 9 and 8 years, respectively, from the first dose of treatment in their respective parent studies.

These results for the Val30Met and non-Val30Met groups included deaths following transplantation or within 30 days after drug discontinuation as part of post-study reporting.

One other study, an observational, multi-institutional, hospital-based cohort study, directly compared survival estimates with tafamidis versus natural disease progression and liver transplant among stage 1 Val30Met patients [10]. The results demonstrated a survival benefit with either tafamidis or liver transplant compared with untreated controls [10]. In addition, tafamidis was associated with a 63% ($p = 0.050$) reduction in risk of death compared with liver transplant in early-onset patients (a corresponding analysis among late-onset patients was not conducted, given the small sample size) [10].

Tafamidis has been shown to delay neurological disease progression in ATTR-PN [20–22] and more recently to reduce the risk of mortality in transthyretin amyloidosis with cardiomyopathy (ATTR-CM) [23]. This study uses existing clinical trial data in ATTR-PN to examine the potential survival benefit in that population. Given the average 3–5 years since onset of symptoms at baseline for patients in the present study (Table 2), and an approximate 10-year estimated survival after disease onset in untreated patients [4], these results indicate that tafamidis may confer a survival benefit in ATTR-PN. In other words, estimates of the median duration from disease onset to death reported in the literature is ~ 10 years (although this can vary considerably based on genotype and phenotype), whereas in the present study, 75–85% of patients treated with tafamidis are still alive ~ 8–9 years after starting tafamidis treatment, which is estimated as ~ 11–14 years after disease onset. Overall, the current analyses offer an important evaluation of patients treated with tafamidis in clinical trials; however, limitations of the analysis are recognized, and longer-term data are needed.

Limitations

The analyses were conducted on longitudinal clinical trial data limited to deaths reported for patients while on study medication as part of standard reporting. As generally encountered with rare diseases, the sample sizes were small (especially for the non-Val30Met group). In addition, a placebo control group was not included in the open-label extension studies. Improvements in standard of care over time may also impact survival estimates [12].

CONCLUSION

Overall, when considering both Val30Met and non-Val30Met patients, the current analysis of long-term tafamidis treatment may suggest favorable patient prognosis. There were very few deaths observed during tafamidis treatment, and none were considered treatment-related. The results are consistent with the beneficial effects of tafamidis in delaying disease progression across Val30Met and nonVal30Met patients [17–21] and its demonstrated real-world effectiveness [15, 24]. Together, these data underscore the importance of early treatment intervention with tafamidis. As ATTR-PN is often misdiagnosed [4, 25, 26], leading to treatment delays, enhanced awareness of the disease and associated “red flag” symptoms are needed [27].

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Compliance with Ethics Guidelines. All study protocols were approved by local institutional review boards and were in compliance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki of 1964, as revised in 2013. All patients provided written informed consent. Further details of this ongoing study, including the progression of patients through the parent and extension studies and the names of institutional review boards or independent ethics committees, are available elsewhere [21, 22].

Data Availability. Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

REFERENCES

1. Planté-Bordeneuve V, Kerschen P. Transthyretin familial amyloid polyneuropathy. Handb Clin Neurol. 2013;115:643–58.

2. Hund E. Familial amyloidotic polyneuropathy: current and emerging treatment options for transthyretin-mediated amyloidosis. Appl Clin Genet. 2012;5:37–41.

3. Koike H, Tanaka F, Hashimoto R, Tomita M, Kawagashira Y, Iijima M, et al. Natural history of transthyretin Val30Met familial amyloid polyneuropathy: analysis of late-onset cases from non-endemic areas. J Neurol Neurosurg Psychiatry. 2012;83:152–8.

4. Ando Y, Coelho T, Berk JL, Waddington Cruz M, Ericzon BG, Ikeda S, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31.

5. Rowczenio DM, Noor I, Gillmore JD, Lachmann HJ, Whelan C, Hawkins PN, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. Hum Mutat. 2014;35:E2403–12.

6. Rowczenio D, Wechalekar A. Mutations in hereditary amyloidosis, 2015. Available from: http://amyloidosismutations.com/mut-attr.php. Accessed 11 Feb 2020.

7. Okamoto S, Wixner J, Obayashi K, Ando Y, Ericzon BG, Friman S, et al. Liver transplantation for familial amyloidotic polyneuropathy: impact on Swedish patients' survival. Liver Transpl. 2009;15:1229–35.

8. Swiecicki PL, Zhen DB, Mauermann ML, Kyle RA, Zeldenrust SR, Grogan M, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. Amyloid. 2015;22:123–31.

9. Mariani LL, Lozeron P, Théaudin M, Mincheva Z, Signate A, Ducot B, et al. Genotype-phenotype correlation and course of transthyretin familial amyloid polyneuropathies in France. Ann Neurol. 2015;78:901–16.

10. Coelho T, Inês M, Conceição I, Soares M, de Carvalho M, Costa J. Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy. Neurology. 2018;91:e1999–2009.

11. Sattianayagam PT, Hahn AF, Whelan CJ, Gibbs SD, Pinney JH, Stangou AJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. Eur Heart J. 2012;33:1120–7.

12. Ericzon BG, Wilczek HE, Larsson M, Wijayatunga P, Stangou A, Pena JR, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? Transplantation. 2015;99:1847–54.

13. Parman Y, Adams D, Obici L, Galán L, Guergueltcheva V, Suhr OB, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol. 2016;29(Suppl 1):S3–13.

14. Suhr OB, Larsson M, Ericzon BG, Wilczek HE, FAPWTR's Investigators. Survival after transplantation in patients with mutations other than Val30Met: extracts from the FAP World Transplant Registry. Transplantation. 2016;100:373–81.

15. Waddington Cruz M, Benson MD. A review of tafamidis for the treatment of transthyretin-related amyloidosis. Neurol Ther. 2015;4:61–79.

16. Coelho T, Merlini G, Bulawa CE, Fleming JA, Judge DP, Kelly JW, et al. Mechanism of action and clinical application of tafamidis in hereditary transthyretin amyloidosis. Neurol Ther. 2016;5:1–25.

17. Coelho T, Maia LF, Martins da Silva A, Waddington-Cruz M, Planté-Bordeneuve V, Lozeron P, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012;79:785–92.

18. Merlini G, Planté-Bordeneuve V, Judge DP, Schmidt H, Obici L, Perlini S, et al. Effects of tafamidis on transthyretin stabilization and clinical outcomes in patients with non-Val30Met transthyretin amyloidosis. J Cardiovasc Transl Res. 2013;6:1011–20.

19. Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Suhr OB, et al. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. J Neurol. 2013;260:2802–14.

20. Waddington Cruz M, Amass L, Keohane D, Schwartz J, Li H, Gundapaneni B. Early intervention with tafamidis provides long term (5.5-year) delay of neurologic progression in transthyretin hereditary amyloid polyneuropathy. Amyloid. 2016;23:178–83.

21. Barroso FA, Judge DP, Ebede B, Li H, Stewart M, Amass L, et al. Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years. Amyloid. 2017;24:194–204.

22. Gundapaneni BK, Sultan MB, Keohane DJ, Schwartz JH. Tafamidis delays neurological progression comparably across Val30Met and non-Val30Met genotypes in transthyretin familial amyloid polyneuropathy. Eur J Neurol. 2018;25:464–8.

23. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379:1007–16.

24. Mundayat R, Stewart M, Alvir J, Short S, Ong ML, Keohane D, et al. Positive effectiveness of tafamidis in delaying disease progression in transthyretin familial amyloid polyneuropathy up to 2 years: an analysis from the transthyretin amyloidosis outcomes survey (THAOS). Neurol Ther. 2018;7:87–101.

25. Koike H, Hashimoto R, Tomita M, Kawagashira Y, Iijima M, Tanaka F, et al. Diagnosis of sporadic transthyretin Val30Met familial amyloid polyneuropathy: a practical analysis. Amyloid. 2011;18:53–62.

26. Adams D, Theaudin M, Cauquil C, Algalarrondo V, Slama M. FAP neuropathy and emerging treatments. Curr Neurol Neurosci Rep. 2014;14:435.

27. Conceição I, Gonzalez-Duarte A, Obici L, Schmidt HH, Simoneau D, Ong ML, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016;21:5–9.