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The Bioequivalence of Tafamidis 61-mg Free Acid Capsules and Tafamidis Meglumine 4 × 20-mg Capsules in Healthy Volunteers

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Abstract

Tafamidis, a non-nonsteroidal anti-inflammatory benzoxazole derivative, acts as a transthyretin (TTR) stabilizer to slow progression of TTR amyloidosis (ATTR). Tafamidis meglumine, available as 20-mg capsules, is approved in more than 40 countries worldwide for the treatment of adults with early-stage symptomatic ATTR polyneuropathy. This agent, administered as an 80-mg, once-daily dose (4 × 20-mg capsules), is approved in the United States, Japan, Canada, and Brazil for the treatment of hereditary and wild-type ATTR cardiomyopathy in adults. An alternative single solid oral dosage formulation (tafamidis 61-mg free acid capsules) was developed and introduced for patient convenience (approved in the United States, United Arab Emirates, and European Union). In this single-center, open-label, randomized, 2-period, 2-sequence, crossover, multiple-dose phase 1 study, the rate and extent of absorption were compared between tafamidis 61-mg free acid capsules (test) and tafamidis meglumine 80-mg (4 × 20-mg) capsules (reference) after 7 days of repeated oral dosing under fasted conditions in 30 healthy volunteers. Ratios of adjusted geometric means (90%CI) for the test/reference formulations were 102.3 (98.0-106.8) for area under the concentration-time profile over the dosing interval and 94.1 (89.1-99.4) for the maximum observed concentration, satisfying prespecified bioequivalence acceptance criteria (90%CI, 80-125). Both tafamidis regimens had an acceptable safety/tolerability profile in this population.

Keywords

transthyretin, amyloidosis, tafamidis, pharmacokinetics, bioequivalence

Transthyretin amyloidosis (ATTR amyloidosis) is a rare, progressive, life-threatening systemic disorder caused by the extracellular deposition and accumulation of transthyretin (TTR) amyloid fibrils within various tissues and organs, resulting in tissue damage and organ failure.[1-3] The native tetrameric structure of TTR, a plasma transport protein for thyroxine and vitamin A, synthesized primarily in the liver,[4] can dissociate into monomers, misfold, and aggregate, leading to amyloidogenesis and degeneration of postmitotic tissue.[5] Patients with ATTR amyloidosis may exhibit a spectrum of clinical features, depending on the site of amyloid deposition, including polyneuropathy (ATTR-PN) and/or cardiomyopathy (ATTR-CM).[6] ATTR-PN is characterized by symptoms of pain and weakness in the lower extremities, sensory loss, and impaired function of the autonomic nervous system.[7] ATTR-CM is an increasingly recognized form of systemic amyloidosis that is typically associated with restrictive cardiomyopathy and heart failure and accompanied by a high risk of atrial fibrillation and heart block, often with preserved ejection fraction.[8]

Tafamidis is a non-nonsteroidal anti-inflammatory benzoxazole derivative that binds with high affinity and

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selectivity to TTR, stabilizing the TTR tetramer, arresting the amyloid cascade, and disrupting the progression of ATTR amyloidosis.[9,10] In a pivotal 18-month, randomized, placebo-controlled trial, tafamidis was shown to reduce neurologic deterioration, preserve nerve function, and maintain quality of life in patients with early-stage ATTR-PN.[11,12] Evidence from the clinical development program, including open-label extension studies providing data from up to 6 years of treatment, and large registry and referral center studies, providing real-world data from up to 10 years, supports the long-term safety and effectiveness of tafamidis in delaying neurologic deterioration and prolonging survival in ATTR-PN.[13-16] In the recent pivotal phase 3 Tafamidis in Transthyretin Cardiomyopathy Trial (ATTR-ACT), tafamidis was associated with lower all-cause mortality and cardiovascular-related hospitalization rates than placebo in patients with ATTR-CM after 30 months of treatment.[17] Use of this TTR stabilizer in amyloid cardiomyopathy led to investigation of its potential effects on the QTc interval. In a randomized, placebo- and positive-controlled study conducted in healthy volunteers, a supratherapeutic single 400-mg oral dose of tafamidis meglumine did not result in prolongation of the QTc interval and was well tolerated.[18]

Studies of tafamidis meglumine 20 mg orally administered once daily as soft gelatin capsules in healthy volunteers have elucidated the drug's clinical pharmacokinetic (PK) profile.[11,19] The drug was shown to be rapidly absorbed, with a median time to maximum concentration of approximately 2 hours, and was highly bound to protein in plasma (>99.5%). The parent compound was the major circulating form of the drug in plasma, and glucuronidation was the major metabolic pathway. Administration with food reduced the rate but not the extent of absorption of tafamidis. Following single and repeated dosing of tafamidis, PK parameters were similar, suggesting that tafamidis had no metabolic induction or inhibition effects. Tafamidis was eliminated slowly, with a mean half-life of approximately 59 hours. After once-daily dosing for 14 days, steady state was reached by day 14, with minimum and maximum steady-state concentrations of 1.6 and 2.7 μg/mL, respectively. Findings from population PK analyses suggested that steady-state clearance of tafamidis was not affected in patients with renal impairment (compared with those with no renal impairment), but systemic exposure was reduced by approximately 40% in patients with moderate hepatic impairment (compared with healthy volunteers). In addition, after repeated once-daily dosing of tafamidis 20 mg, clearance was 19% slower and maximum steady-state concentration 21% higher in patients older than 60 years of age compared with those younger than 60 years of age.

After its introduction, tafamidis was initially only available as 20-mg micronized tafamidis meglumine capsules. In ATTR-ACT, patients received 20-mg (tafamidis meglumine 1 × 20-mg and 3 × placebo) or 80-mg (tafamidis meglumine 4 × 20-mg) doses of tafamidis.[17] Given that the higher tafamidis dose was under investigation (and is now approved in the United States, Japan, Canada, and Brazil) for the treatment of ATTR-CM, development of a single tafamidis meglumine 80-mg capsule was initiated for patient convenience, but a final product could not be attained because of technical limitations (ie, concentration-dependent gelling in aqueous media). An alternative single solid oral dosage formulation, tafamidis 61-mg free acid capsules, with systemic exposure comparable to the tafamidis meglumine 80-mg dose, was developed as a more convenient dosing option (and is now approved for the treatment of ATTR-CM in the United States, United Arab Emirates, and European Union).

The tafamidis 61-mg free acid capsule presentation was selected based on simulations as well as PK and safety data from prior single-dose studies of tafamidis. The tafamidis free acid and meglumine salt formulations share the same mechanisms of action and biologic effects. In this open-label, multiple-dose, phase 1 bioequivalence study, we compared the rate and extent of absorption of the test formulation, tafamidis 61-mg free acid capsules, with those of the reference formulation, tafamidis meglumine 80-mg (4 × 20-mg) capsules, under fasted conditions in healthy volunteers to assess their relative bioavailability.

Subjects and Methods

Study Population

Healthy, nonsmoking volunteers of both sexes, aged 18-55 years, with a total body weight > 50 kg (110 lb) and body mass index (BMI) ≥ 17.5 and ≤ 30.5 kg/m^2, were eligible for enrollment. Eligibility was also based on findings from medical history, physical examination, vital signs, clinical laboratory testing, and electrocardiograms (ECGs). If fertile, male volunteers were eligible only if willing and able to use effective contraception; female volunteers were eligible only if they were not of childbearing potential. Individuals were ineligible if they had taken an investigational drug within 30 days, an herbal supplement or hormone replacement therapy within 28 days, or a prescription or nonprescription drug or dietary supplement within 7 days of receiving the first dose of study drug.

Study Design and Procedures

The study protocol was approved by the independent ethics committee at the single investigational site where the study was conducted (Comite d'Ethique

Hospitalo-Facultaire Saint-Luc, Brussels, Belgium). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. All participants in this study provided written informed consent before screening.

The clinical segment of this single-center, open-label, randomized, 2-period, 2-sequence, crossover, multiple-dose bioequivalence study was conducted at the Pfizer Clinical Research Unit, Brussels, Belgium. Clinical laboratory samples were analyzed at the Institut de Biologie Clinique in Brussels, Belgium.

Potential participants were screened up to 28 days before randomization and, if eligible, were randomized to 1 of 2 treatment sequences: test → reference or reference → test. After an overnight fast of at least 10 hours, participants received tafamidis 61-mg free acid capsules (Pfizer; batch no. 17-002147) or tafamidis meglumine 4 × 20-mg capsules (Pfizer; batch no. 16-005246) each morning at least 1 hour before breakfast on days 1-6, and 4 hours before breakfast on day 7 (the final treatment day) in each period. On the first 2 days of treatment, they took a second dose approximately 12 hours after the first dose, following a fast of at least 2 hours. The twice-daily regimen on day 1 and day 2 was implemented to reduce the time required for the study drug to reach steady state. Participants were allowed to drink water without restriction on days 1-6 but not from 1 hour predose to 1 hour postdose on day 7. Because serial PK sampling started on day 7, participants also could not lie down, eat, or drink beverages (except water as described) for 4 hours after receiving treatment on that study day. Participants could be discharged after final assessments on day 8. A 16-day washout period separated each treatment period.

Drug/PK Analysis

Blood samples were collected from participants in labeled dipotassium ethylenediaminetetraacetic acid tubes to harvest plasma for PK assessment before administration of the study drug on day 6; predose, and 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 hours postdose on day 7; and 24.0 hours postdose on day 8 of each treatment period. The plasma samples were stored at approximately −10°C to −30°C prior to analysis and assayed by Covance Bioanalytical Services LLC (Indianapolis, Indiana) using a validated liquid chromatography-mass spectrometry method. Tafamidis (PF-06291826) and its internal standard (PF-06474853-00, with stable isotopes labeled) were isolated from 50 μL of human plasma using a protein precipitation extraction procedure, with 50 μL of internal standard solution and 300 μL of acetonitrile. After vortexing and centrifugation, 200 μL of water was added, and the resulting supernatant was transferred to a 96-well plate and analyzed by electrospray ionization liquid chromatography coupled with tandem mass spectrometry in negative ionization mode. The chromatographic separation was achieved using Atlantis dC_{18} columns (50 × 2.1 mm, 5-μm particle size; Waters Corporation, Milford, Massachusetts) and gradient elution. Components of mobile phase solvents A and B were water:formic acid (100%:0.1%) and acetonitrile:methanol:formic acid (50%:50%:0.1%), respectively. (Additional information on the analysis method used, ie, mobile phase flow rates, mass spectrometer parameters, and mass/charge number, is provided in the supplementary online appendices.) The calibration standard curve ranged from 10 to 10 000 ng/mL, with a lower limit of quantification for tafamidis at 10 ng/mL. For the clinical study sample analysis, between-day accuracy for the quality control levels (low, medium, medium high, high, and diluted) ranged from −3.3% to 3.0%, and precision was ≤7.2%.

The steady-state PK parameters evaluated were time of maximum measured plasma concentration (T_{max}), area under the concentration-time profile over the dosing interval (AUC_{tau}), and maximum observed concentration (C_{max}). These PK parameters were calculated for each participant and each tafamidis formulation.

Statistical Methods

Thirty healthy volunteers (15 per treatment sequence) were enrolled to ensure a PK-evaluable sample of 26 participants (13 per treatment sequence). The study had at least 90% power to demonstrate the bioequivalence of the test and reference treatments for both AUC_{tau} and C_{max}.

All participants who had evaluable PK data were included in the PK analyses. PK parameters were estimated using standard noncompartmental methods. Median values (range) were reported for T_{max}; geometric means were calculated for AUC_{tau} and C_{max} for tafamidis 61-mg free acid capsules and tafamidis meglumine 4 × 20-mg capsules, with variability based on geometric percentage coefficient of variation (%CV).

Natural log-transformed AUC_{tau} and C_{max} on day 7 were analyzed separately using a mixed-effects model, with sequence, period, and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (test/reference) and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and 90%CIs for the differences were exponentiated to provide estimates of the ratios of adjusted geometric means (test/reference) and 90%CIs for the ratios. The prespecified bioequivalence acceptance criterion was a 90%CI contained between 80% and 125% for the ratios of adjusted geometric means for AUC_{tau} and C_{max} of the 2 tafamidis formulations.

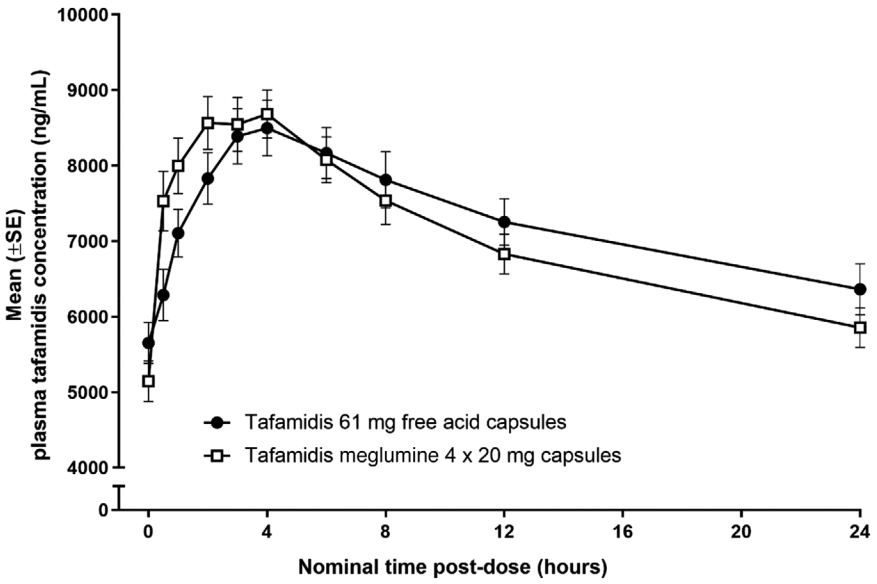

Figure 1. Plasma tafamidis concentration-time profiles after multiple oral doses on day 7 by treatment group.

Table 1. Summary of Plasma Tafamidis PK Parameter Values by Treatment Group

Parameter		Tafamidis 61-mg Free Acid Capsules (n = 30)	Tafamidis Meglumine 4 × 20-mg Capsules (n = 30)
AUC_{tau}, ng·h/mL	Mean (SD)	174 400 (42 139)	169 600 (35 637)
	Median (range)	166 000 (112 000-285 000)	171 000 (125 000-258 000)
	Geometric mean (%CV)	170 000 (23)	166 200 (20)
	Ratio of adjusted geometric mean (90%CI)	102.3 (98.0-106.8)	
C_{max}, ng/mL	Mean (SD)	8778 (2089)	9241 (1796)
	Median (range)	8100 (5250-13 700)	8950 (6580-14 600)
	Geometric mean (%CV)	8553 (23)	9087 (18)
	Ratio of adjusted geometric mean (90%CI)	94.1 (89.1-99.4)	
T_{max}, h	Median (range)	4.0 (2.0-8.0)	2.0 (0.5-6.0)

Participants who received at least 1 dose of study drug were analyzed for safety and tolerability, assessed primarily by monitoring adverse events (AEs) throughout the study. Clinical laboratory tests, ECGs, and physical examinations were performed and vital signs measured on the first day (day 1) and last day (day 8) of each treatment period.

Results

Thirty healthy volunteers enrolled and received treatment in the study, and all completed the study. Fifteen followed each of the 2 treatment sequences (ie, tafamidis 61-mg free acid capsules → tafamidis meglumine 4 × 20-mg capsules; tafamidis meglumine 4 × 20-mg → tafamidis 61-mg free acid capsules). All participants were men, with a mean age of 39 years (range, 18-55 years), weight of 79 kg, and BMI of 25.2 kg/m^2, and most were white (26 [87%]).

Mean concentration-time profiles for the tafamidis 61-mg free acid and tafamidis meglumine 4 × 20-mg capsules were very similar (Figure 1). The steady-state PK parameters for these formulations are summarized in Table 1. The median (range) T_{max} was 4.0 hours (2.0-8.0 hours) and 2.0 hours (0.5-6.0 hours) for the tafamidis 61-mg free acid and tafamidis meglumine 4 × 20-mg capsules, respectively. Geometric mean AUC_{tau} values (geometric %CV) were 170 000 ng·h/mL (23) and 166 200 ng·h/mL (20), respectively; and C_{max} values were 8553 ng/mL (23) and 9087 ng/mL (18). The ratios of adjusted geometric means (90%CIs) for the test/reference formulations were 102.3 (98.0-106.8) for AUC_{tau} and 94.1 (89.1-99.4) for C_{max}. Because the 90%CIs were contained within the 80% to 125% range,

the test formulation satisfied the prespecified bioequivalence criteria relative to the reference formulation.

The overall incidence of AEs was similar for the tafamidis 61-mg free acid and tafamidis meglumine 4 × 20-mg capsules (n = 10 [33%] and n = 12 [40%], respectively). Headache was the most common AE, reported by 5 participants after receiving either tafamidis regimen. No participants died during the study, had serious treatment-related AEs, or discontinued treatment because of AEs. In addition, no clinically relevant changes were observed with either formulation in clinical laboratory parameters, vital signs, ECGs, or physical examinations.

Discussion

In this phase 1 study, a new formulation of tafamidis (tafamidis 61-mg free acid capsule) was demonstrated to be bioequivalent, as measured by AUC_{tau} and C_{max}, to the standard marketed formulation (tafamidis meglumine 80-mg [4 × 20-mg] capsules) after repeated oral dosing for 7 days in a population of healthy volunteers. The 90%CIs for the ratios of adjusted geometric means for both AUC_{tau} and C_{max} for the test/reference formulations were contained within the 80% to 125% range, satisfying prespecified bioequivalence criteria. In addition, multiple doses of both formulations administered under fasted conditions had an acceptable safety/tolerability profile, with no serious AEs, deaths, or discontinuations because of AEs reported in the study.

A notable strength of this multiple-dose bioequivalence study is that its design and methodology, including the criteria used to define bioequivalence, are appropriate based on guidance from the US Food and Drug Administration.[20] Moreover, the study reflects collaboration with the Scientific Advice Working Party of the European Medicines Agency. However, in other countries, a multiple-dose design may not be preferred, and a single-dose design may be favored because of perceived greater sensitivity to detect differences between formulations. Given the long half-life, appreciable accumulation at steady state, and intended once-daily chronic use of tafamidis, comparison of the steady-state PK parameters across test and reference formulations is considered a clinically relevant approach to demonstrating bioequivalence. Establishing bioequivalence based on steady-state data provides a more clinically relevant comparison of exposure between the test and reference formulations than the single-dose data.

Tafamidis meglumine 20 mg once daily is approved in more than 40 countries globally for the treatment of ATTR-PN in adults with early-stage symptomatic polyneuropathy to delay peripheral neurological impairment. Tafamidis in an 80-mg daily dose is also approved for the treatment of both hereditary and wild-type ATTR-CM in adults to decrease all-cause mortality and cardiovascular-related hospitalization in the United States, Japan, Canada, and Brazil and is under regulatory review in multiple other countries. Availability of the single solid tafamidis 61-mg free acid formulation, shown in this study to be bioequivalent to tafamidis meglumine administered as 4 × 20-mg capsules and currently approved in the United States, United Arab Emirates, and European Union, provides a more convenient dosing option for patients with ATTR-CM.

Conflicts of Interest

P.A. Lockwood, V.H. Le, M.T. O'Gorman, T.A. Patterson, M.B. Sultan, E. Tankisheva, Q. Wang, and S. Riley are full-time employees of Pfizer and hold Pfizer stock and/or stock options.

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Data Sharing

On 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 deidentified 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 United States and/or European Union or (2) in programs that have been terminated (ie, 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 deidentified 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 requesters must enter into a data access agreement with Pfizer.

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