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The effect of tafamidis on the QT_c interval in healthy subjects

Karen J. Klamerus,[1] Eric Watsky,[2]* Robert Moller,[2] Ronnie Wang[2] & Steve Riley[2]

[1]Pfizer, Inc., San Diego, CA and [2]Pfizer, Inc., Groton, CT, USA

Correspondence
Dr Karen J. Klamerus PharmD, Pfizer, Inc., 10646 Science Center Drive (CB10), San Diego, CA 92121, USA.
Tel.: +858 638 3848
Fax: +877 481 3398
E-mail: karen.klamerus@pfizer.com

*Affiliation at the time the study was conducted.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Treatment options for transthyretin (TTR) amyloidosis are limited, with liver/heart transplantation the standard of care.
- Cardiomyopathy is a common presentation of TTR amyloidosis.
- A thorough QT study in healthy volunteers was conducted to assess the potential for QT_c prolongation to be associated with treatment with tafamidis, a TTR stabilizer, at supra-therapeutic concentrations.

WHAT THIS STUDY ADDS

- The study demonstrated that administration of a supra-therapeutic, single 400 mg oral dose of tafamidis solution does not prolong the QT_c interval in healthy volunteers.
- No difference between tafamidis and placebo was observed in adverse events, supporting the overall safety profile of tafamidis.

AIMS

The transthyretin (TTR) stabilizer, tafamidis, has demonstrated efficacy and safety in the treatment of TTR familial amyloid polyneuropathy (20 mg day^{-1}). Tafamidis use in TTR cardiomyopathy led to the study of the potential effect of tafamidis on the QT_c interval in healthy subjects.

METHODS

This randomized, three treatment, three period, six sequence crossover study with placebo, a positive control (moxifloxacin 400 mg) and tafamidis (400 mg, to achieve a supra-therapeutic C_{max} of ~20 μg ml^{-1}) was conducted in healthy volunteers at three clinical research units. Oral dosing in each of the three treatment periods was separated by a washout period of ≥14 days. Serial triplicate 12-lead electrocardiograms were performed. QT_c intervals were derived using the Fridericia correction method. Safety and tolerability were assessed by physical examination, vital signs measurement, laboratory analyses and monitoring of adverse events (AEs).

RESULTS

A total of 42 subjects completed the study. The upper limit of the two-sided 90% confidence intervals (CIs) for the difference in baseline-adjusted QT_cF between tafamidis 400 mg and placebo was <10 ms (non-inferiority criterion) for all time points. The lower limit of the two-sided 90% CI between moxifloxacin 400 mg and placebo exceeded 5 ms at the pre-specified moxifloxacin t_{max} of 3 h post-dose, confirming assay sensitivity. C_{max} and AUC(0,24 h) for tafamidis were 20.36 μg ml^{-1} and 305.4 μg ml^{-1} h, respectively. There were no serious/severe AEs or treatment discontinuations due to AEs.

CONCLUSIONS

This thorough QT_c study suggests that a supra-therapeutic single 400 mg oral dose of tafamidis does not prolong the QT_c interval and is well-tolerated in healthy volunteers.

Introduction

Transthyretin (TTR) amyloidosis is both an inherited and an age-related amyloidosis that is a progressively debilitating and ultimately fatal condition. The most common phenotypic presentations of TTR amyloidosis are a sensorimotor and autonomic polyneuropathy [TTR familial amyloid polyneuropathy (TTR-FAP)] and cardiomyopathy (TTR-CM) [1].

The TTR protein (known as pre-albumin) is a tetrameric liver transport protein for thyroxine and the retinol-binding protein–retinol (vitamin A) complex [2–5], that

under normal conditions circulates as a tetramer, but genetic mutation and ageing results in tetramer dissociation into unstable monomers that form insoluble amyloid fibrils that accumulate and produce deleterious effects on tissues and organ function [6–10].

TTR amyloidosis results in autonomic dysfunction and conduction abnormalities as well as the development of a restrictive cardiomyopathy in TTR-CM with progressive loss of cardiovascular function resulting from myocardial accumulation of amyloid fibrils. Echocardiographic findings in TTR-CM include thickened ventricular walls (concentric hypertrophy), a normal or mildly reduced left ventricular ejection fraction, increased myocardial echogenicity, atrioventricular valve and interatrial septal thickening, often with evidence of restricted diastolic dysfunction [11].

Current treatment options for patients with TTR amyloidosis are limited, with liver transplant the standard of care for mild or moderate TTR-FAP, and heart transplant for amyloidosis patients with advanced heart failure. Liver transplant does not effectively prevent cardiomyopathy in most cases and is not recommended for patients with late-stage disease [12].

TTR stabilizers, such as tafamidis, which target the rate-limiting step in the formation of amyloid fibrils, represent a novel pharmacologic therapy for TTR amyloidosis [10, 13]. TTR-stabilizing agents can be prescribed at an early stage of disease prior to liver transplantation or may potentially delay the need for liver transplant [12].

Tafamidis is approved for the treatment of TTR-FAP in Europe, Japan, Mexico and Argentina, and is the first pharmacotherapy for TTR-FAP to slow the progression of peripheral neurologic impairment. Tafamidis specifically binds to the two thyroxine binding sites on TTR, increasing tetramer stability and inhibiting the dissociation of TTR into monomers [1]. By inhibiting TTR amyloid formation, tafamidis has the potential to delay the progression of TTR-amyloid disease, with no activity anticipated for other types of amyloidoses associated with proteins other than TTR.

The efficacy and safety of tafamidis 20 mg day^{-1} have been demonstrated in clinical trials [14–16], where tafamidis stabilized tetrameric TTR and slowed the progression of peripheral neurologic impairment in patients with TTR-FAP carrying the Val30Met mutation [15], and was well-tolerated and effectively stabilized TTR in patients with non-Val30Met TTR mutations [16]. These evaluations of tafamidis have suggested low risk for affecting the QT interval [14–16].

Considering the autonomic nervous system involvement associated with TTR-FAP and the predominant cardiac involvement in TTR-CM and the risk for conduction abnormalities in that patient population, a thorough QT study of tafamidis in healthy volunteers was conducted to assess the potential for corrected QT interval (QT_c) prolongation to be associated with treatment with tafamidis. In accordance with International Conference on Harmonization (ICH) E14 recommendations [17], a placebo control was included to enhance the validity of the study and to avoid potential biases inherent in the study procedures. Moxifloxacin, a positive control, was included to provide confidence that the study could detect a QT_c prolongation of clinical importance, since it demonstrates at least a 5 ms mean effect on QT/QT_c.

The primary objective of this study was to demonstrate the effect of a supra-therapeutic concentration of tafamidis (~20 μg ml^{-1}) on the QT_c interval in healthy subjects.

Methods

Subjects and study design

This was a randomized, three treatment, three period, six sequence crossover study with placebo as well as a positive-control (moxifloxacin) and tafamidis in healthy volunteers, conducted at three separate clinical research units (CRUs) located in the United States (US), Belgium and Singapore, from January 2013 through to April 2013. In each treatment period, subjects were admitted to the CRU the day prior to dosing and discharged after completing all trial procedures for that period on the morning of day 2 (24 h post-dose). There was a washout period of at least 14 days between dosing in each of the three treatment periods.

The protocol and informed consent documentation were approved by the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) at each of the investigational centres participating in the study. The study was performed in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and with Good Clinical Practice (GCP) guidelines, and, where applicable, local country regulations relevant to the use of new therapeutic agents in the countries of conduct. All subjects provided written informed consent. The study was registered at clinicaltrials.gov under registration no. NCT01775761.

A total of 42 healthy, non-smoking men and women of non-childbearing potential (post-menopausal or documented hysterectomy and/or bilateral oophorectomy) between the ages of 18 and 55 years inclusive (US and Belgium CRUs), or between the ages of 21 and 55 years inclusive (Singapore CRU), with a body mass index (BMI) of 17.5 to 30.5 kg m^{-2} and a total body weight of >50 kg were treated. To ensure a healthy population, subjects underwent screening that included a detailed medical history, physical examination, including vital signs measurement, 12-lead electrocardiogram (ECG) and clinical laboratory tests.

Subject exclusion criteria for the study included evidence or history of clinically significant haematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic or allergic diseases (including drug allergies, but excluding untreated,

asymptomatic, seasonal allergies at the time of dosing), which would potentially interfere with the conduct or interpretation of the study, any condition affecting drug absorption; use of tobacco/nicotine products, history of regular alcohol consumption within 6 months of screening [>7 drinks week^{-1} for women and >14 drinks week^{-1} for men (US CRU) or >14 drinks week^{-1} for women and >21 drinks week^{-1} for men (Belgium and Singapore CRUs)], treatment with an investigational drug within 30 days or five half-lives, blood pressure (BP) ≥ 140 mmHg (systolic) or ≥90 mmHg (diastolic), QT_c >450 ms or QRS interval >120 ms, use of prescription or non-prescription drugs or dietary supplements within 7 days or five half-lives prior to the first study dose, blood donation (~500 ml) within 56 days prior to the first dose, history of sensitivity or intolerance to quinolone antibiotics, including moxifloxacin, or heparin or heparin-induced thrombocytopenia, treatment with moxifloxacin within 1 week prior to the first study dose, history of risk factors of QT prolongation or torsades de pointes, congenital deafness and family history of sudden death or any other severe acute or chronic medical/psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or affect interpretation of study results.

Treatment regimen

To adequately assess potential QT prolongation, a supratherapeutic dose was needed to provide a mean maximum concentration (C_{max}) of at least 18 μg ml^{-1} which was approximately three-fold higher than the expected mean maximum steady-state tafamidis concentration at the highest planned clinical dose (60 mg once daily) in a phase 3 TTR-CM study. Additionally, to maintain a five-fold safety margin based upon preclinical studies, the highest allowable mean C_{max} was 25 μg ml^{-1}. Given the target concentrations for this QT study and the preclinical safety margins, a target mean C_{max} of 20 μg ml^{-1} was selected. A previous unpublished study confirming the pharmacokinetics (PK), safety and tolerability of tafamidis demonstrated that a tafamidis solution of 400 mg in 240 ml water was required to achieve the target supratherapeutic concentration (data on file, Pfizer, Inc [18]).

In the current study, tafamidis 400 mg (solution) or placebo were orally administered as a single dose on day 1, after an 8 h overnight fast. Treatment assignments to tafamidis and placebo were double-blinded to the subjects, investigator and CRU staff (except the pharmacist) but open to the sponsor. Single dose moxifloxacin 400 mg administration was unblinded. Study medication was administered with room temperature water to a total volume of 240 ml. Subjects were randomized to each of the treatment sequences and dosing in each of the three treatment periods was separated by a washout period of at least 14 days, which is more than five times longer than the 59 h pharmacokinetic half-life of tafamidis.

ECG

The primary ECG endpoint was the baseline-adjusted, time-matched mean differences in QT_c interval, using Fridericia's correction method (QT_cF), between tafamidis and placebo at each post-dose time. The secondary ECG endpoint was the baseline-adjusted, mean difference in QT_cF between moxifloxacin and placebo at the historical moxifloxacin median t_{max} of 3 h [19].

Triplicate 12-lead ECGs were obtained during screening, on day 1 (pre-dose and post-dose) and on day 2 or upon early termination. The ECGs were obtained after the subject had rested in the supine position for ≥10 min. Triplicate ECGs (separated by 2–4 min intervals) were collected at −1, −0.5 and 0 h pre-dose on day 1 of each period with the average of the means obtained from the three sets of triplicate measurements within each period serving as each subject's baseline QT_c value for that period. When timing of ECG measurements coincided with blood collection, the ECG measurement was performed prior to blood collection to minimize the risk of vagal effects associated with phlebotomy.

A semi-automated approach was used to evaluate ECG tracings. This technique uses a computer algorithm for the initial placement of reference marks on the waveforms to note where on the tracing the computer is making its measurements, based upon the global waveforms from all 12-leads. A qualified investigator then reviewed the placement of the reference marks on the ECG tracing, and performed adjustments when the computerized measurements were considered to be inaccurate, based upon prospectively defined criteria for determining when changes to computer-generated marks were warranted. When leads were removed from subjects, markings were made to ensure consistent placement. Any significant morphological observation noted by the investigator was reflected in the ECG interpretation.

QT_cF intervals were derived using Fridericia's heart rate (HR) correction formula:

$$QT_cF\,(\text{ms}) = \text{QT interval}\,(\text{ms})/\text{RR interval}\,(\text{RR})^{1/3},$$
$$\text{where RR}\,(\text{s}) = 60/\text{HR}.$$

QT_cB intervals were derived using Bazett's heart rate correction formula:

$$QT_cB\,(\text{ms}) = \text{QT interval}\,(\text{ms})/\text{RR}^{1/2},$$
$$\text{where RR}\,(\text{s}) = 60/\text{HR}.$$

Visual inspection of the scatter plot of QT_cF *vs.* RR using placebo and baseline data indicated that the linear relationship between QT and RR was effectively corrected using QT_cF compared with QT_cB, as QT_cF displayed less correlation with RR ($r = 0.113$) compared with QT_cB ($r = 0.479$). QT_cF was therefore deemed appropriate as the primary correction.

Statistical analysis of QT/QT_c

A sample size of 42 completers provided 99% power to exclude a 10 ms mean difference from placebo at each time point if the expected mean difference was ≤5 ms between tafamidis and placebo at each time point. The overall study power was at least 93% for eight post-dose time points.

With the intersection–union test, no adjustment to the level of significance was made for multiple comparisons and each test was at the 5% alpha level. To demonstrate assay sensitivity in the study, with a one-sided alpha of 0.05, data from 42 subjects provided at least 99% power to detect that the lower bound of the two-sided 90% confidence interval (CI) for mean differences between moxifloxacin and placebo was >5 ms at the anticipated moxifloxacin median t_{max} (3 h). The power calculation assumed a common intra-subject standard deviation (SD) of 5.35 ms on post-dose QT_cF, obtained as an average from eight thorough QT studies from the CRUs where the study was conducted. A lack of effect of tafamidis on the QT_c interval was to be concluded if the upper bound of the two-sided 90% (equivalent to one-sided 95%) CIs for all the time-matched mean differences between tafamidis and placebo were <10 ms. The study would be deemed sufficiently sensitive to detect QT/QT_c prolongation if the lower bound of the two-sided 90% CI for mean differences between moxifloxacin and placebo was >5 ms at 3 h post-dose of moxifloxacin.

The raw post-dose QT_cF intervals were analyzed using a mixed effect model with sequence, period, treatment, time and treatment-by-time interaction as fixed effects, subject within sequence as a random effect and baseline QT_cF as a covariate. Estimates of the adjusted mean differences (Test–Reference) and the two-sided 90% CIs for each treatment and time were obtained from the model. The mixed effects model was implemented using SAS PROC MIXED [20] with restricted maximum likelihood (REML) estimation method, compound symmetry assumed for the variance-covariance structure of the i^{th} subject between observations in different periods as well as in the same period at different times, and Kenward-Roger degrees of freedom algorithm.

For the primary ECG analysis, the raw post-dose QT_cF of the single supra-therapeutic dose of tafamidis was the Test while that of placebo was the Reference. For the secondary ECG analysis, the raw post-dose QT_cF of moxifloxacin 400 mg was the Test while that of placebo was the Reference. Changes from baseline for QT_cF, uncorrected QT, pulse rate (PR), QRS interval and HR were summarized descriptively and categorically.

PK sampling and analyses

Blood samples (4 ml) to provide approximately 1.5 ml of plasma for PK analysis were collected into tubes containing potassium ethylene-diamine-tetraacetic acid prior to dosing and at 1, 1.5, 2, 3, 4, 6, 12 and 24 h post-dose. Samples were centrifuged at 1700 *g* for 10 min at 4°C and plasma was stored at −20 ± 10°C within 1 h of collection. Plasma samples were analyzed for tafamidis concentrations (Covance, Indianapolis, IN, USA) by high-performance liquid chromatography tandem mass spectrometry using a validated analytical method. Calibration standard responses were in the range 3.0–3000 ng ml^{-1} (or diluted if above range) using a quadratic ($L/concentration^2$) least-squares regression. The lower limit of quantification (LLOQ) for tafamidis was 3.0 ng ml^{-1}. The between-day assay accuracy, expressed as percent relative error, for quality control (QC) concentrations ranged from −2.0 to 0.7% for the low, medium, high and diluted QC samples. Assay precision, expressed as the between-day percent coefficients of variation (%CV) of the mean estimated concentrations of QC samples was ≤5.8 for low (9.0 ng ml^{-1}), medium (150 ng ml^{-1}), high (2250 ng ml^{-1}) and diluted (15 000 ng ml^{-1}) concentrations.

Tafamidis PK parameters were calculated for each subject receiving tafamidis treatment using non-compartmental analysis of plasma concentration−time data. C_{max} and t_{max} were observed directly from data and area under the concentration−time curve from 0 to 24 h (AUC(0,24 h)) was determined using a linear/log trapezoidal method.

Safety assessment

The safety and tolerability of tafamidis was assessed by physical examination, adverse event (AE) monitoring (voluntarily reported or observed), 12-lead ECG, vital sign measurement (BP and PR) and clinical safety laboratory measurements. For all AEs, sufficient information was obtained to determine the causality of the AE. Any events that occurred following the start of treatment or that increased in severity were classified as treatment-emergent adverse events (TEAEs). Events that occurred in a non-treatment period (for example, washout or follow-up) following a treatment period were considered treatment-emergent and attributed to the previous treatment taken. A serious AE (SAE) was defined as any AE that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant disability/incapacity or resulted in congenital anomaly/birth defect. The assessment of whether an AE was treatment-related was made by the investigational site physicians, who were blinded to treatment assignment.

Results

Demographics

In total, 42 subjects (41 males, one female) were randomized, received study drug and were analyzed for PK and

safety. Most subjects were white or Asian, with a mean age of 36.2 years, and had a mean weight of 77.6 kg and BMI of 25.2 kg m^{-2} (Table 1). There were a total of 16 protocol deviations, the majority of which were due to incorrect laboratory analyses/procedures.

ECG

The scatter plot of QT_cF *vs.* RR using placebo and baseline data indicated that the linear relationship between QT and RR was effectively corrected using QT_cF (r = 0.113) (unpublished data on file, Pfizer, Inc.) [21].

Time-matched baseline-adjusted least-squares mean differences between tafamidis 400 mg and placebo, and moxifloxacin 400 mg and placebo, *vs.* time post-dose for QT_cF with 90% CI are shown in Figure 1.

A summary of statistical analysis of tafamidis 400 mg compared with placebo for baseline-adjusted QT_cF at each post-dose time point is provided in Table 2. At all post-dose time points, the upper limit of the two-sided 90% (equivalent to one-sided 95%) CI was <10 ms (highest value was +0.86 ms). There was no clinically relevant effect of a single supra-therapeutic dose of tafamidis (400 mg) *vs.* placebo on time-matched QT_cF intervals. The adjusted mean difference in QT_cF intervals between moxifloxacin 400 mg and placebo was 9.76 ms (90% CI 7.65, 11.87) at 3 h post-dose of moxifloxacin's historic population t_{max}. Thus, this study was deemed adequately sensitive since the lower limit of the two-sided 90% CI was >5 ms.

An absolute maximum QT_cF interval of 450–480 ms was not observed in subjects receiving tafamidis 400 mg or placebo and was observed in two (4.8%) subjects receiving moxifloxacin 400 mg. No subjects had a QT_cF interval ≥480 ms. None of the subjects receiving tafamidis 400 mg had a maximum increase from baseline ≥30 ms for QT_cF interval.

Table 1

Demographic characteristics

Demographic characteristic	Male (*n* = 41)	Female (*n* = 1)	Total (*n* = 42)
Age			
Mean, years (SD)	36 (9)	53 (0)	36 (10)
Range, years	21–55	53–53	21–55
Race, *n*			
White	18	1	19
Black	5	0	5
Asian	17	0	17
Other	1	0	1
Weight, mean kg (SD)	78 (10)	61 (0)	78 (11)
BMI, mean kg m^{-2} (SD)	25 (3)	22 (0)	25 (3)

BMI, body mass index; SD, standard deviation.

PK parameters

Following administration of a single oral dose of tafamidis 400 mg, absorption was rapid to moderate with a median (range) t_{max} of 2 h (1–6 h) post-dose. Plasma concentrations declined steadily with measurable concentrations up to 24 h post-dose (Figure 2). Exposures as measured by C_{max} and geometric mean AUC(0,24 h) for tafamidis were 20.36 μg ml^{-1} and 305.4 μg ml^{-1} h, respectively. Inter-subject variability for C_{max} and AUC (0,24 h), based on geometric %CV values, was 18% and 15%, respectively.

Safety and tolerability

A summary of the incidence of AEs is provided in Table 3. There were no SAEs, severe AEs or discontinuations of treatment due to an AE. Ten subjects receiving

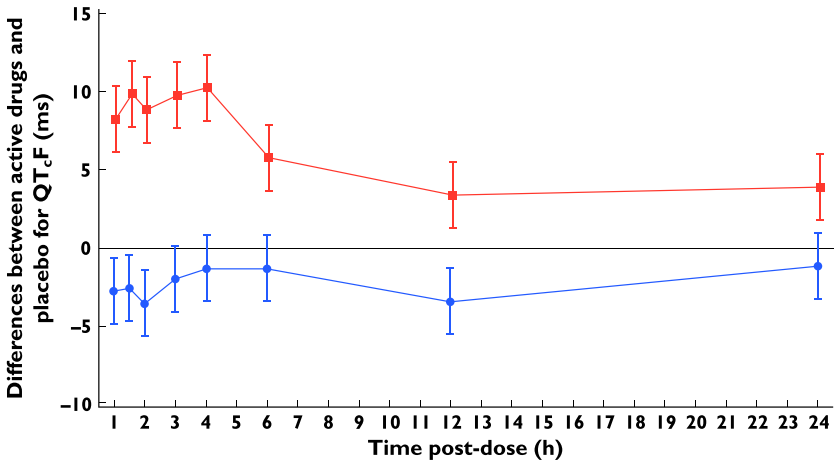

Figure 1

Time-matched baseline adjusted least squares mean differences between tafamidis 400 mg and placebo, and moxifloxacin 400 mg and placebo for QT_cF. ●–●–●, tafamidis 400 mg; ■–■–■, moxifloxacin 400 mg. Circles and squares represent the baseline adjusted mean differences and vertical lines represent 90% confidence intervals obtained from mixed effect model. Mean of triplicate collections at each time point was used in the analysis

Table 2

Summary of statistical analysis of tafamidis 400 mg compared with placebo for QT_cF

Time post-dose (h)	Baseline-adjusted least squares means Tafamdis (ms) (n = 42)	Placebo (ms) (n = 42)	Difference (Tafamidis – Placebo) (ms)	90% CI (ms)
1	407.85	410.64	−2.79	−4.89, −0.69
1.5	408.65	411.30	−2.65	−4.75, −0.55
2	408.43	412.07	−3.64	−5.74, −1.54
3	408.39	410.43	−2.04	−4.14, 0.06
4	409.58	410.97	−1.38	−3.48, 0.72
6	403.51	404.91	−1.39	−3.50, 0.71
12	405.12	408.61	−3.49	−5.59, −1.39
24	407.61	408.85	−1.24	−3.35, 0.86

CI, confidence interval; QT_cF, QT interval using Fridericia's correction method. Mean of triplicate collections at each time point was used in the analysis.

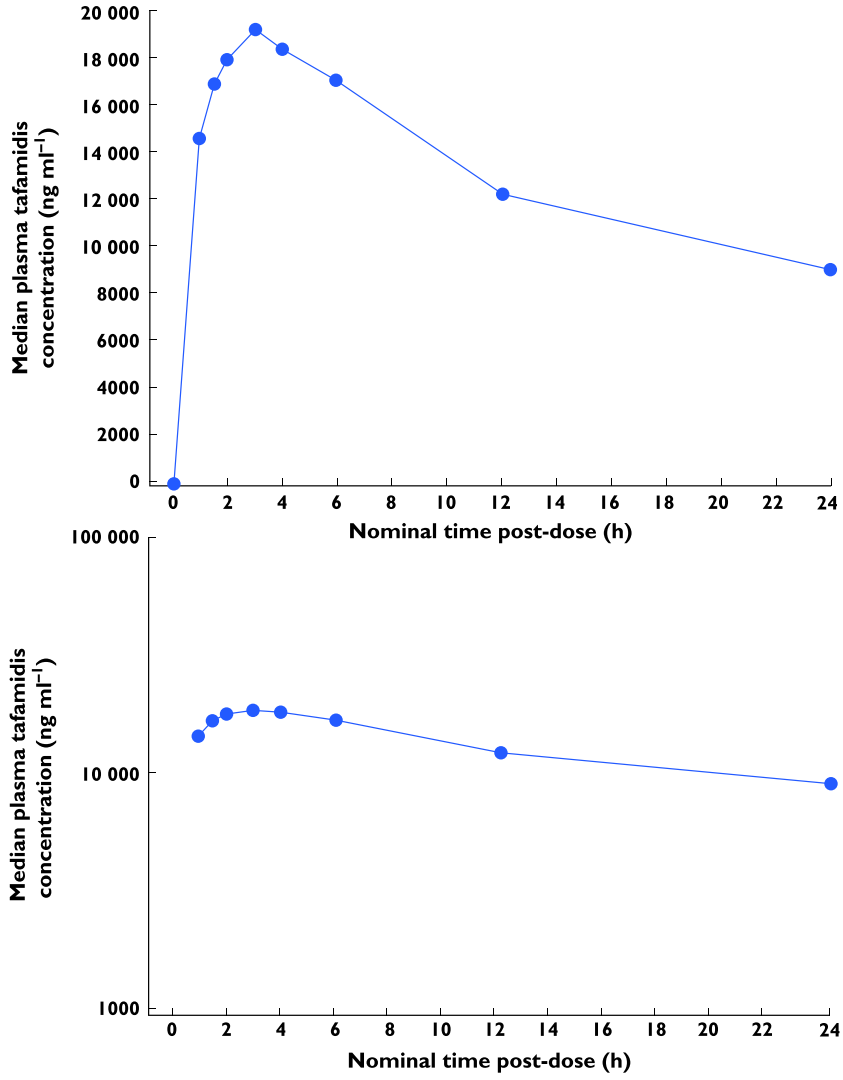

Figure 2

Plasma tafamidis concentration–time profile following single oral doses of tafamidis 400 mg (linear and log scales for median plasma concentrations of tafamidis). —●—, tafamidis 400 mg. The lower limit of quantification for the measurement of tafamidis concentrations was 3.0 ng ml^{-1}

Table 3

Summary of treatment-emergent adverse events: all causality (treatment-related)

Number of subjects with events (Total subjects evaluable for AEs)	Tafamidis 400 mg (n = 42)	Moxifloxacin 400 mg (n = 42)	Placebo (n = 42)
Number of AEs	14 (9)	18 (11)	12 (9)
Subjects with AEs	10 (7)	12 (8)	9 (6)
Subjects with AE leading to discontinuation	0	0	0
Number of subjects with most frequent AEs*			
Acne	2 (2)	1 (1)	3 (3)
Headache	2 (2)	1 (1)	2 (2)
Nausea	0	3 (3)	1 (1)
Dizziness	0	2 (2)	0

AE, adverse event. *Occurring in >one subject.

tafamidis 400 mg reported 14 TEAEs, of which nine TEAEs were treatment-related. Twelve subjects receiving moxifloxacin 400 mg reported 18 TEAEs, of which 11 TEAEs were treatment-related. Nine subjects receiving placebo reported 12 TEAEs, of which nine TEAEs were treatment-related. Most TEAEs were mild in severity, and the most frequently reported TEAEs across all three treatment groups were acne, headache and nausea.

Discussion

The results of this thorough QT_c study conducted across three separate sites in the US, Belgium and Singapore demonstrate that the administration of a supra-therapeutic, single, 400 mg oral dose of tafamidis solution did not prolong the QT_c interval in healthy volunteers. The upper bounds of the two-sided 90% CIs were less than 10 ms for all baseline-adjusted, time-matched mean differences between tafamidis and placebo, thereby fulfilling the criteria for a negative QT/QT_c study. Single doses of moxifloxacin 400 mg established that the study had adequate sensitivity to detect increases in QT_c.

Linear regression of C_{max} *vs*. tafamidis dose from a previous study [18] predicted that a single dose of tafamidis 400 mg would achieve the target supra-therapeutic concentration (mean C_{max} 20 μg ml^{-1}). In this study, tafamidis 400 mg achieved a mean C_{max} of 20.36 μg ml^{-1} which represents an approximately 7.5-fold margin above the mean maximum steady-state exposure with the currently approved oral 20 mg tafamidis dose. The supra-therapeutic single dose was well-tolerated in healthy volunteers, consistent with expectations from phase 1 dose escalation studies and phase 2/3 studies in patients with TTR-FAP who received 20 mg tafamidis as a once daily dose [14–16]. AEs observed in this study by organ system were consistent with the safety profile demonstrated in previous phase 2/3 studies of tafamidis 20 mg once daily [14–16].

Limitations

Thorough QT_c studies such as this one are usually performed in healthy volunteers who constitute the ideal population for determining whether the study drug has an effect on QT prolongation, as they are not being treated with concomitant medications, have no electrolyte abnormalities that would be expected to affect cardiac conduction and do not have T-wave abnormalities. Patients with TTR amyloidosis may present with autonomic nervous system or cardiac conduction abnormalities or have comorbidities or may be taking concomitant medications that impact upon cardiac conduction. Both male and female healthy volunteers were permitted to be recruited for this study. However, as females were required to be of non-childbearing potential, only one of the subjects enrolled was female. It is therefore difficult to definitively conclude from the data from this study whether a comparable lack of effect on the QT_c interval would be seen in females, but there are no data to suggest the effect would be different. This study was conducted at three sites (which followed the same standard operating procedures). However an analysis was not performed to ascertain whether effects observed were consistent across sites.

In conclusion, results from this randomized, three treatment, three period, six sequence crossover study in healthy volunteers demonstrate that treatment with tafamidis does not prolong the QT interval and are supportive of the overall favourable safety profile of tafamidis.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare KK, EW, RM, RW and SR received support from Pfizer, Inc. for the submitted work, KK, EW, RM, RW and SR are current employees of Pfizer, Inc. and EW was an employee of Pfizer Inc. within the last 3 years and at the time the study was conducted. There are no other relationships or activities that could appear to have influenced the submitted work.

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