Received: 17 March 2021 | Revised: 1 July 2021 | Accepted: 7 July 2021

DOI: 10.1111/cts.13116

ARTICLE

# Absence of effect of steady state bempedoic acid on cardiac repolarization: Results of a thorough QT/QTc study in healthy volunteers

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**Funding information**
This study was supported by Esperion Therapeutics, Inc., Ann Arbor, MI.

## Abstract

Bempedoic acid is an inhibitor of adenosine triphosphate–citrate lyase approved for use in adults with hypercholesterolemia. Nonclinical studies assessed binding to the human ether-a-go-go–related gene (hERG) potassium channel in vitro and the effect of bempedoic acid on QT/QTc in cynomolgus monkeys. A randomized, double-blind, parallel-design clinical study assessed the effects of steady-state bempedoic acid at a supratherapeutic dose (240 mg/day, 33.3% higher the180 mg/day therapeutic dose), placebo, and moxifloxacin (400 mg) in healthy subjects. In vitro binding potency for bempedoic acid to the hERG potassium channel was weak, with half-maximal inhibition ($IC_{50}$) estimated at greater than 1000 μM (>1670-fold the bempedoic acid 180 mg/day steady-state unbound maximum concentration). In monkeys, individual rate-corrected QT intervals showed no time- or dose-dependent changes up to 100 mg/kg of bempedoic acid. In human subjects, the upper 90% confidence interval (CI) for the difference in QTc interval, corrected using Fridericia's formula (QTcF), between bempedoic acid and placebo was less than 5 msec at all time points. Concentration-QTcF analysis showed that maximum bempedoic acid concentration at steady-state was attained at a median 2.1 h postdose, and the predicted mean change (90% CI) in QTcF at the observed mean bempedoic acid concentration 2 h postdose was −0.5 (−5.0, 4.0) msec. The lower bound of the moxifloxacin 90% CI exceeded 5 msec at prespecified time points, establishing study sensitivity. Steady-state bempedoic acid at a supratherapeutic dose of 240 mg was generally well-tolerated and not associated with QTc prolongation in healthy subjects.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Drug-induced QT prolongation is associated with a rare and potentially fatal ventricular arrhythmia known as torsades de pointes. As a result, it is now a

standard regulatory requirement for drug candidates to undergo assessment of QT prolongation risk.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

Bempedoic acid is an inhibitor of adenosine triphosphate (ATP)–citrate lyase that is chronically administered to patients at risk for or with cardiovascular disease for the treatment of hypercholesterolemia. This phase I study assessed whether steady-state concentrations of bempedoic acid at a supratherapeutic dose of 240 mg is associated with increased risk of prolongation of ventricular repolarization.

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

This study demonstrated that steady-state concentrations of bempedoic acid and its active metabolite ESP15228 were not associated with QT/QTc interval prolongation in 54 healthy subjects who received bempedoic acid 240 mg once daily for 9 days. This study adds supportive cardiac safety information for the safe and efficacious use of bempedoic acid in patients with cardiovascular disease.

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**

In vitro human ether-a-go-go–related gene (hERG) binding and results in cynomolgus monkeys indicated that bempedoic acid has a favorable cardiac electrocardiographic nonclinical safety profile. These nonclinical results are consistent with the findings of a clinical study in which bempedoic acid at a supratherapeutic dose level was generally well-tolerated and not associated with QTc prolongation in healthy subjects.

## INTRODUCTION

Numerous drugs and drug candidates have been associated with cardiac toxicity, including QT prolongation, a serious adverse effect that can result in deadly cardiac ventricular arrhythmias (e.g., torsades de pointes).[1,2] The QT interval, the time from initiation of the QRS complex to the end of the T-wave in the heart's electrical cycle, represents a summary of the ventricular myocyte action potential.[1] The rapid- and slow-activating components of the delayed rectifier-potassium current, $I_{Kr}$ and $I_{Ks}$, influence the duration of the action potential and the QT interval. The human ether-a-go-go-related gene (*hERG*) and *KVLQT1* gene encode for the human potassium channel–forming proteins responsible for $I_{Kr}$ and $I_{Ks}$, respectively, and are commonly involved in the mechanism of drug-induced QT prolongation.[3,4] Based on these safety risks, it is now a standard regulatory requirement that drug candidates undergo assessment for QT prolongation risk.[5,6]

Bempedoic acid is an oral, once-daily, adenosine triphosphate (ATP)–citrate lyase inhibitor that is approved to treat hypercholesterolemia. In the United States, bempedoic acid is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of low-density lipoprotein cholesterol.[7] In phase III clinical trials, bempedoic acid significantly lowered low-density lipoprotein cholesterol after 12 weeks in patients with hypercholesterolemia compared with placebo.[8–11] Bempedoic acid was also generally well-tolerated with comparable rates of treatment-emergent adverse events (TEAEs), muscle-related adverse events (AEs), and discontinuations between bempedoic acid and placebo treatment groups.[8–11] The effect of bempedoic acid on cardiovascular morbidity and mortality has not been determined.

This report is a summary of nonclinical and phase I clinical studies investigating the potential for QT prolongation associated with bempedoic acid use. In accord with the US Food and Drug Administration (FDA) guidelines for assessments of QT prolongation,[4,5] bempedoic acid studies included: (1) an in vitro evaluation of the effects on hERG potassium channels,[3] (2) an in vivo cardiovascular (QT interval) safety study in cynomolgus monkeys, and (3) a phase I clinical trial evaluating the effect of steady-state bempedoic acid on cardiac repolarization in healthy male and female subjects at a supratherapeutic dose of bempedoic acid.

# METHODS

## Nonclinical studies

The in vitro inhibition of the rapidly activating delayed rectifier cardiac potassium current ($I_1$) by bempedoic acid binding to the ion channel encoded by *hERG* was evaluated. Cell membranes derived from human embryonic kidney (HEK)-293 cells and stably transfected with *hERG* cDNA (ChanTest Corporation, Cleveland, OH) were incubated with bempedoic acid (0, 10, 100, 300, and 1000 μM) or terfenadine (0.060 μM) and percent inhibition of hERG channel activity was calculated.

The potential cardiovascular effects of bempedoic acid were evaluated in conscious freely moving cynomolgus monkeys (MPI Research, Inc, Mattawan, MI). Four male monkeys were fitted with radio transmitters to acquire electrocardiography (ECG) tracings from 2 h to at least 20 h postdose. Each monkey received vehicle (0 mg/kg) and bempedoic acid (10, 30, and 100 mg/kg), administered in ascending order with 7 days between treatments. Rate-corrected QT intervals were calculated using the method of Miyazaki and Tagawa,[12] and serum cardiac troponin I concentrations were determined within 2 h of the end of the 22-h monitoring period. All monkeys were observed for morbidity, mortality, and injury. Nonhuman primate use was approved by the Institutional Animal Care and Use Committee (IACUC) and carried out in accordance with the Guide for the Care and Use of Laboratory Animals by the National Institutes of Health.

## Phase I clinical study

### Study design and treatments

A phase I, single-center, randomized, double-blind, placebo- and positive-controlled, parallel-design study was performed to evaluate cardiac repolarization in healthy subjects at a supratherapeutic bempedoic acid dose of 240 mg/day. The study was conducted in accord with the Good Clinical Practice guideline as defined by the International Conference on Harmonisation, The Declaration of Helsinki, all applicable federal regulations, as appropriate, and approved by the Chesapeake Institutional Review, Columbia, MD. All subjects provided written informed consent before taking part in the study. The study was conducted at Spaulding Clinical Research, LLC, West Bend, WI.

Subjects were randomized 1:1:1 to receive one of the following once-daily oral treatments: treatment A, bempedoic acid 240 mg plus moxifloxacin-matched placebo on days 1 to 9; treatment B, bempedoic acid–matched placebo plus moxifloxacin-matched placebo on days 1 to 9; or treatment C, bempedoic acid–matched placebo plus moxifloxacin-matched placebo on days 1 to 8 and moxifloxacin 400 mg plus bempedoic acid–matched placebo on day 9. Subjects were fasted overnight for at least 10 h before receiving assigned treatments on the morning of days −1, 1, and 9; fasting was continued for 4 h after dosing on days 1 and 9.

### Subjects

The study enrolled male and nonpregnant female volunteers aged 18–50 years, with body mass index of 18 to 33 kg/m$^2$, who were judged to be healthy based on medical history, physical examinations, and routine laboratory tests. Subjects were excluded if there was evidence of clinical disease; abnormalities observed on physical examination or in laboratory values; history of risk factors for QT prolongation or torsades de pointes; abnormal findings at ECG screening; corrected QT interval using Fridericia's formula (QTcF) greater than 430 msec (men) or 450 msec (women); systolic blood pressure greater than 150 mmHg or less than 90 mmHg; diastolic blood pressure greater than 95 mmHg or less than 50 mmHg; positive serology for human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C antigen; evidence of illicit drug use; recent participation in an investigational drug trial; or previous treatment with bempedoic acid.

### Pharmacodynamic assessments

Continuous 12-lead ECG tracings were acquired after at least 10 min of rest with the patient in a supine position using a MortaraX12+ digital recorder (Mortara Instrument, Inc., Milwaukee, WI). Triplicate ECG measurements were averaged for each time point at predose and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, and 24 h after dosing with bempedoic acid on days 1 and 9, plus additional measurements at 36 and 48 h after day 9 dose administration. Digital ECGs were transmitted to a central ECG laboratory and QT intervals were measured using automated technologies with manual over-read by readers blinded to treatment, time, and study day identifiers. Time-matched baseline measurements were acquired before the first dose of bempedoic acid (day −1). The measured QT was corrected (QTc) for heart rate (HR) before analysis using Fridericia's formula ($QTcF = QT/RR^{0.33}$). Estimates of time-matched dQTcF were calculated for individual subjects as the difference between QTcF at each postdose time point on day 9 less the corresponding time-matched QTcF on day −1. The primary end point ddQTcF was defined for subjects in the bempedoic acid and moxifloxacin

treatment groups as the difference between dQTcF minus the average dQTcF of the subjects receiving placebo at each postdose time point.

### Pharmacokinetic assessments

Serial blood samples were collected following predose and postdose ECG measurements at the same time points to evaluate the pharmacokinetics (PKs) of bempedoic acid and the active ESP15228 metabolite. Plasma concentrations were determined using validated bioanalytical methodology and PK parameters of maximum concentration ($C_{max}$), and time to $C_{max}$ ($T_{max}$), area under the concentration-time curve (AUC) from zero to 24 h ($AUC_{0-24}$), AUC from zero to the last measured concentration ($AUC_{0-t}$), and trough concentrations were determined by noncompartmental analysis (Phoenix WinNonlin version 6.3).

### Safety and tolerability

AEs and TEAEs were monitored from the time of informed consent to 7 days after the final dose was received. The intensity of each AE was characterized by the investigator as mild, moderate, or severe, and the degree of relatedness to the study drug was judged by the investigator as not related, possibly related, probably related, or definitely related.

### Pharmacodynamics

The primary analysis included a comparison of time-matched differences in baseline adjusted QTcF intervals between bempedoic acid 240 mg and placebo at each postdose time point. A mixed-effects model was used to evaluate ddQTcF, including terms for baseline QTcF, study drug (bempedoic acid or placebo), postdose ECG assessment time point, study drug-by-postdose ECG time point interaction, and subject as a random effect. A time-dependent, first-order autoregressive covariance designed for unequally spaced time points was applied to the model and the upper 95% one-sided confidence interval (CI) of ddQTcF was used to make the primary statistical comparison.

Secondary analyses included evaluations of ECG variables, dQTc, and ddQTc between the bempedoic acid and placebo groups and between the moxifloxacin and placebo groups. Adequate assay sensitivity of the mixed-effects model was determined by a lower one-sided 95% CI greater than 5 msec for changes in moxifloxacin ddQTcF after application of the Hochberg adjustment for at least one prespecified time point at 1, 2, or 4 h after dosing.

### Pharmacokinetic–pharmacodynamic relationships

Graphic and mixed-effects analyses were performed to evaluate the relationships between bempedoic acid and ESP15228 exposure in plasma and QT/QTc response. A linear mixed-effects model was used to characterize the relationship between ddQTcF and corresponding time-matched bempedoic acid and ESP15228 plasma concentrations on days 1 and 9 in subjects randomized to receive bempedoic acid 240 mg/day.

The average of triplicate QTc values at each time point were used to estimate the predicted population mean ddQTcF and its corresponding upper 95% one-sided CI over a range of observed plasma concentrations. All analyses were conducted with SAS version 9.3 or later (SAS Institute, Inc., Cary, NC).

### Determination of sample size

The size of each treatment arm was sufficient to reject the null hypothesis, in which the upper limit of a one-sided 95% CI of ddQTcF exceeded 10 msec, with at least 85% power and assuming a maximum treatment effect of 2 msec and early termination rate of ~ 5%.

## RESULTS

### Nonclinical studies

Binding of bempedoic acid to the hERG potassium channel expressed in HEK-293 cell membranes indicated a weak interaction at the highest bempedoic acid concentration tested, with 5.4% ± 0.4% inhibition observed at 1000 μM (Table S1). The half-maximal inhibitory concentration ($IC_{50}$) of bempedoic acid was estimated to be greater than 1000 μM (345 μg/ml). Binding of the metabolite ESP15228 to the hERG potassium channel was not evaluated.

In monkeys, there were no significant changes in HR, blood pressure, or ECG intervals related to bempedoic acid treatments of 10, 30, and 100 mg/kg. Individual rate-corrected QT intervals did not show time- or dose-dependent changes over the 0 to 100 mg/kg range (Figure S1). Cardiac troponin I serum concentrations after bempedoic acid 100 mg/kg treatment were similar to concentrations after vehicle treatment.

## Phase I clinical study

### Subject disposition and demographics

A total of 162 subjects were enrolled in the study. One subject (treatment A, bempedoic acid) withdrew from study participation, one subject (treatment B, placebo) was discontinued due to a TEAE related to increased hepatic enzymes, and 160 completed the study. Overall, mean (± SD) age was 34.6 (± 9.8) years and body mass index was 27.1 (± 3.6) kg/m$^2$; most subjects were men (67.3%), racial distribution was roughly even (45.7% Black and 46.9% White), and 14.2% were Hispanic/Latino. Participant demographics were similar across each of the treatment groups, except a higher proportion of women (42.6%) and slightly lower proportion of Whites (40.7%) in the moxifloxacin group (Table 1).

### Pharmacodynamic results

The adequacy of the correction formula was determined by linear regression analysis of QTcF-RR matched data from days −1, 1, and 9 for subjects in the bempedoic acid, placebo, and moxifloxacin treatment groups. Regression analysis of QTcF-RR–matched data concluded a slope of 0.001 and y-intercept of 400.3 msec, indicating estimates of QTcF were independent of RR interval (abscissa) and supported the use of Fridericia's formula to correct QT intervals for changes in HR across subjects and evaluate drug-induced QT prolongation.

Estimates of absolute QTcF interval did not exceed 450 msec at any time point among subjects who received bempedoic acid (treatment A) but was observed at two time points in treatment B, and four time points in treatment C groups. Changes from baseline in QTcF did not exceed 30 msec in the treatment A or B groups, but changes greater than 30 msec were observed at four time points in the treatment C group. Estimates of QTcF greater than 480 msec and changes from baseline in QTcF greater than 60 msec were not observed. Comparisons of mean ddQTcF profiles across treatment groups indicated no clinically significant changes in QT/QTc were associated with bempedoic acid dosing (Figure 1). Among subjects who received treatment A, mean changes in ddQTcF following a single bempedoic acid 240 mg dose were similar to the mean ddQTcF profile recorded in subjects who received treatment B on day 1. For the 24-h period following day 9 dosing, ddQTcF remained below 10 msec for subjects who had received once-daily bempedoic acid 240 mg for 9 days (treatment A) and were nonoverlapping with the ddQTcF profile of subjects after single moxifloxacin 400-mg dose administration on day 9 (treatment C; Figure 1). Based on the mixed-effects model of ddQTcF, small positive and negative changes were associated with bempedoic acid 240 mg on day 9 and the upper 90% confidence bounds were below 5 msec at all time points (Table 2). By comparison, increases in ddQTcF occurred at all time points between 1 and 16 h postdose (90% CI excluded zero) following moxifloxacin dosing (treatment C). Adequate assay sensitivity was demonstrated in mixed-effects models of ddQTcF as the lower bound of the moxifloxacin 90% CI exceeded 5 msec at the 2-h and 4-h prespecified time points. Changes in HR were comparable between the placebo and bempedoic acid arms and were not clinically significant. However, HR increased modestly in the moxifloxacin arm. Minimal changes in the PR interval were observed and the change was similar across the three treatment groups. The QRS interval was not significantly affected by any of the treatments in this study.

**TABLE 1** Participant demographics

| Parameter | Bempedoic acid 240 mg ($n = 54$) | Placebo ($n = 54$) | Moxifloxacin 400 mg ($n = 54$) | Overall ($N = 162$) |
|---|---|---|---|---|
| Age, years, mean (SD) | 32.5 (9.7) | 35.1 (10.3) | 36.1 (9.2) | 34.6 (9.8) |
| BMI, kg/m$^2$, mean (SD) | 27.4 (3.5) | 26.8 (3.7) | 27.1 (3.7) | 27.1 (3.6) |
| Female, *n* (%) | 15 (27.8) | 15 (27.8) | 23 (42.6) | 53 (32.7) |
| Race, *n* (%) | | | | |
| Black | 24 (44.4) | 26 (48.1) | 24 (44.4) | 74 (45.7) |
| White | 27 (50.0) | 27 (50.0) | 22 (40.7) | 76 (46.9) |
| Other[a] | 3 (5.6) | 1 (1.9) | 8 (14.8) | 12 (7.4) |
| Ethnicity, *n* (%) | | | | |
| Hispanic or Latino | 9 (16.7) | 6 (11.1) | 8 (14.8) | 23 (14.2) |

Abbreviation: BMI, body mass index.

[a]Other indicates Asian, Native American, Alaskan Native, Native Hawaiian, Other Pacific Islander, or Other.

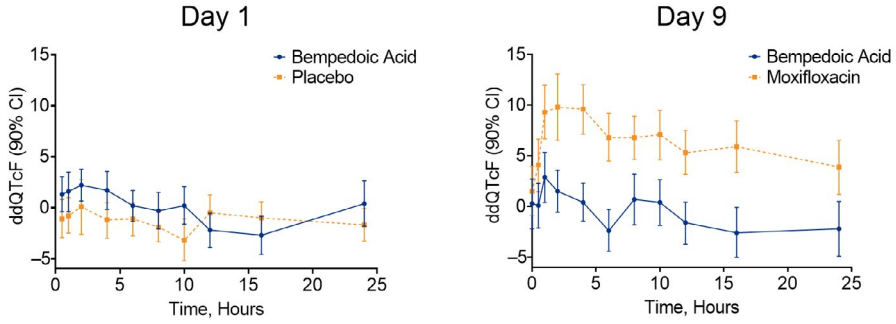


**FIGURE 1** Effects of bempedoic acid and moxifloxacin on QT interval corrected by Fridericia's formula in human subjects. Day 1 represents subjects treated with bempedoic acid (treatment A) or bempedoic acid–matched placebo plus moxifloxacin-matched placebo (treatment C), whereas day 9 represents subjects who received once-daily bempedoic acid for 9 days (treatment A) compared with subjects who received a single moxifloxacin dose (treatment C). CI, confidence interval; ddQTcF, time-matched placebo- and baseline-adjusted QTcF interval; QTcF, QT interval corrected by Fridericia's formula

**TABLE 2** Mixed-effects model results for placebo-corrected estimates of baseline-adjusted QTcF of day 9 steady-state bempedoic acid 240 mg and single-dose moxifloxacin 400 mg

| Time, hours | ddQTcF (msec) | | | |
|---|---|---|---|---|
| | Bempedoic acid 240 mg | | Moxifloxacin 400 mg | |
| | Mean | 90% CI | Mean | 90% CI |
| 0.5 | −1.6 | −6.2, 2.9 | 3.8 | −0.7, 8.3 |
| 1 | 0.2 | −4.3, 4.8 | 9.3[a] | 4.8, 13.8 |
| 2 | −0.5 | −5.0, 4.0 | 9.6[a] | 5.1, 14.1 |
| 4 | −1.1 | −5.6, 3.5 | 10.2[a] | 5.7, 14.8 |
| 6 | −4.1 | −8.6, 0.5 | 7.6[a] | 3.1, 12.1 |
| 8 | −1.7 | −6.3, 2.8 | 6.7[a] | 2.2, 11.3 |
| 10 | −2.5 | −7.0, 2.1 | 7.8[a] | 3.3, 12.3 |
| 12 | −3.4 | −8.0, 1.1 | 5.5[a] | 0.9, 10.0 |
| 16 | −4.4 | −8.9, 0.1 | 6.1[a] | 1.6, 10.6 |
| 24 | −3.6 | −8.2, 0.9 | 4.2 | −0.3, 8.7 |

Abbreviations: CI, confidence interval; QTcF, QT interval corrected by Fridericia's formula.

[a]Value is significant (90% CI excludes zero).

## Pharmacokinetic results

Bempedoic acid and ESP15228 plasma concentration-time profiles following 9 days of oral bempedoic acid 240 mg are shown in Figure 2. Peak levels of bempedoic acid were attained by a median time of 2.1 h after dosing. Mean estimates of $C_{max}$ and $AUC_{0-24}$ on day 9 were ~ 1.8- and 2.5-fold greater than corresponding exposure parameters on day 1, respectively (Table 3). Bempedoic acid concentrations reached steady-state after 7 days, as suggested by the similarity between 24-h mean trough concentrations on day 7 (12.6 μg/ml) and day 9 (13.7 μg/ml). Bempedoic acid protein binding determined by equilibrium dialysis

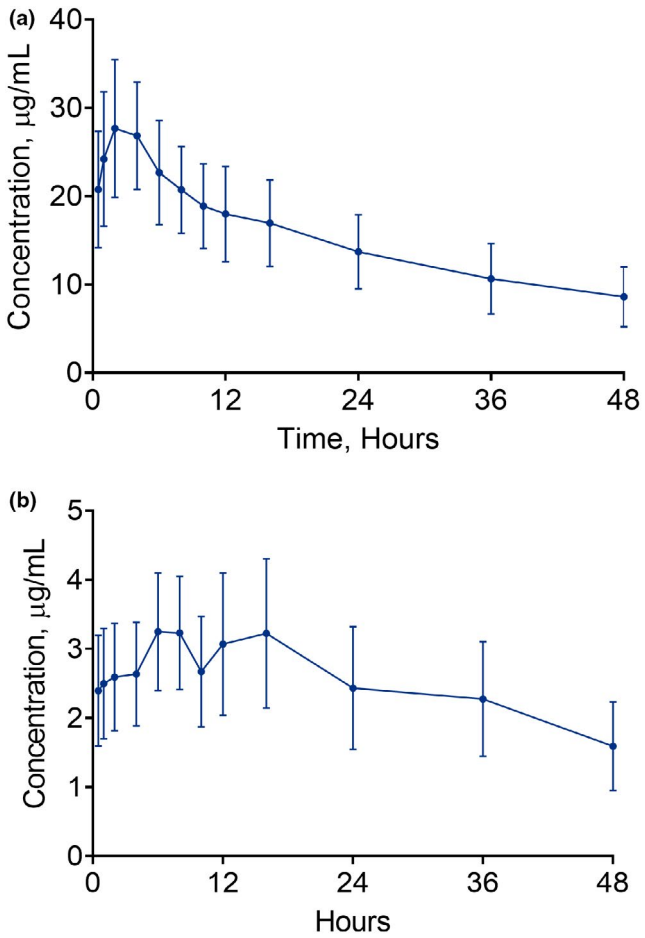


**FIGURE 2** Mean (± SD) plasma concentration-time profiles of bempedoic acid (a) and ESP15228 (b) in human subjects on day 9. Data are presented as the mean ± SD ($n = 53$)

in human plasma was ~ 99.3% bound. At steady-state, total mean $C_{max}$ was 30.4 μg/ml and unbound $C_{max}$ was 0.304 μg/ml, assuming a 1% unbound fraction.

Maximum ESP15228 concentrations were attained by a median 8.1 h after bempedoic acid dosing on day 9 and

**TABLE 3** Summary of bempedoic acid and ESP15228 pharmacokinetic parameters after single and once daily repeat bempedoic acid 240-mg dose administration

| Parameter | Mean (CV%) | | | |
|---|---|---|---|---|
| | Bempedoic acid | | ESP15228 | |
| | Day 1 ($n = 54$) | Day 9 ($n = 52$) | Day 1 ($n = 54$) | Day 9 ($n = 52$) |
| $C_{max}$, μg/ml | 17.3 (24.5) | 30.4 (20.2) | 1.0 (21.6) | 3.6 (27.7) |
| $T_{max}$, h[a] | 2.3 (1.1, 8.1) | 2.1 (1.1, 4.1) | 12.1 (6.1, 24.1) | 8.1 (4.1, 16.1) |
| $AUC_{0-t}$, h·μg/ml | 188.2 (19.9) | 730.8 (27.0) | 17.4 (20.6) | 122.0 (31.3) |
| $AUC_{0-24}$, h·μg/ml | 187.7 (20.0) | 465.9 (23.7) | 17.3 (20.6) | 69.8 (29.1) |
| $C_{24}$, μg/ml | 4.6 (27.6) | 13.7 (31.0) | 0.7 (24.3) | 2.4 (36.6) |
| M/P[b] $AUC_{0-24}$ ratio | – | – | 0.092 | 0.150 |

Abbreviations: $AUC_{0-t}$, area under the plasma concentration-time curve from time 0 to last measurable concentration; $AUC_{0-24}$, area under the plasma concentration-time curve from time 0 to 24 h; $C_{max}$, maximum plasma concentration; $C_{24}$, trough concentration at 24 h postdose; CV%, percent coefficient of variation; M/P, metabolite/parent ratio; $T_{max}$, time to $C_{max}$.

[a]Values are median (range).

[b]Metabolite (ESP15228)/parent (bempedoic acid).

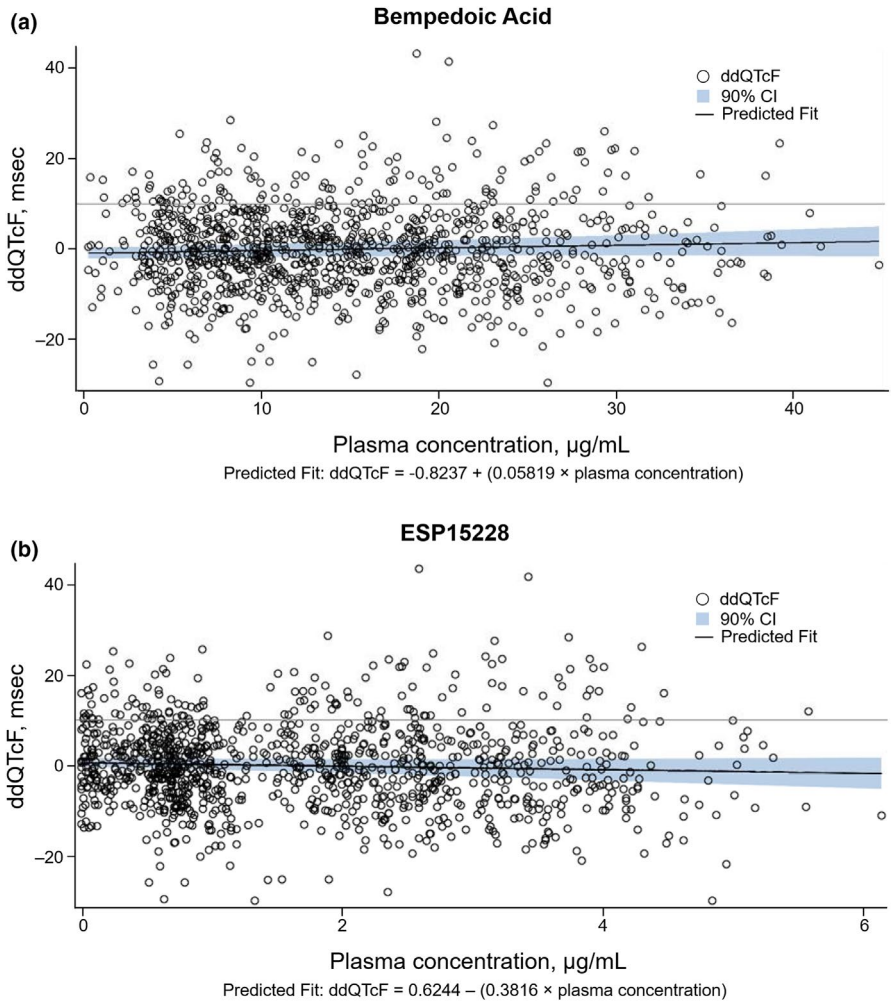


**FIGURE 3** Model-predicted ddQTcF response and 90% confidence interval (CI) versus bempedoic acid (a) and ESP15228 (b) plasma concentrations on days 1 and 9 in human subjects randomized to receive bempedoic acid 240 mg/day. Horizontal line represents change of 10 msec. ddQTcF, time-matched placebo- and baseline-adjusted QTcF interval; QTcF, QT interval corrected by Fridericia's formula

were ~ 3.6-fold higher than on day 1. Mean estimates of metabolite $AUC_{0-24}$ were ~ 4.0-fold higher on day 9 than on day 1. ESP15228 $AUC_{0-24}$ estimates were ~ 9.2% and 15.0% of bempedoic acid $AUC_{0-24}$ exposures on days 1 and 9, respectively. Steady-state metabolite ESP15228 concentrations were attained by day 9 after ~ 7 half-lives

had elapsed, based on an estimated elimination half-life of 28.8 h.[13]

### Pharmacokinetic-pharmacodynamic relationships

The effects of bempedoic acid and ESP15228 exposures on ddQTcF were evaluated by regression analysis using a linear mixed-effects model (Figure 3). Linear regression of ddQTcF over the observed range of bempedoic acid concentrations determined a slope of 0.06 msec per μg/ml and no significant changes in QTc were identified. Similarly, no significant changes in QTc were observed due to ESP15228. For both bempedoic acid and ESP15228, the upper 90% confidence boundary of ddQTcF was consistently below 10 msec and based on the 90% CI, the slopes were not significantly different from zero.

### Safety and tolerability

Overall, 26 (16.0%) of 162 subjects reported at least one TEAE (Table 4). A higher percentage of subjects in the moxifloxacin group (20.4%) reported TEAEs compared with TEAEs reported in the placebo (14.8%) or bempedoic acid (13.0%) groups. The most common TEAEs overall were medical device site reaction (mild skin irritation at electrode site), dysmenorrhea, and dizziness. All TEAEs were considered mild in intensity except for one incidence of muscle weakness of moderate intensity in the bempedoic acid group. One participant in the placebo group had a TEAE of increased hepatic enzyme levels that led to study drug discontinuation. There were no serious AEs or deaths in the study.

## DISCUSSION

This analysis describes the findings from nonclinical and clinical risk assessments of the effect of bempedoic acid on QT/QTc interval prolongation. After repeat administration of a supratherapeutic dose of bempedoic acid, circulating concentrations of bempedoic acid and ESP15228 were not associated with QT/QTc interval prolongation in healthy subjects.

When selecting a bempedoic acid 240-mg dose, 1.33-fold greater than the approved 180 mg bempedoic acid dose, we considered clearance pathways, weighed the potential for food and PK drug interactions, and identified covariates that have the greatest effect on exposure. Bempedoic acid can be taken without regard for food and food does not have an impact on plasma concentrations. The primary mechanism of elimination is through direct glucuronidation by UDP-glucuronosyltransferase-2B7 (UGT2B7). In a clinical study of UGT inhibition by probenecid, the effect on bempedoic acid led to a weak interaction (<2-fold), where an approximate 20% increase in bempedoic acid $C_{max}$ occurred. In addition, there are no known currently available drugs or genetic polymorphisms that would be expected to result in significant drug-drug or pharmacogenomic interactions with bempedoic acid (>2-fold increase in exposure) that might elevate plasma concentrations to levels greater than those observed at the 240-mg dose. The most significant covariate of bempedoic acid PK is moderate renal impairment,

**TABLE 4** Safety

| Parameter | Subjects, *n* (%) | | | |
|---|---|---|---|---|
| | Bempedoic Acid 240 mg (*n* = 54) | Placebo (*n* = 54) | Moxifloxacin 400 mg (*n* = 54) | Overall (*N* = 162) |
| With ≥1 TEAE | 7 (13.0) | 8 (14.8) | 11 (20.4) | 26 (16.0) |
| With ≥1 related TEAE | 6 (11.1) | 5 (9.3) | 8 (14.8) | 19 (11.7) |
| With a TEAE leading to study discontinuation | 0 | 1 (1.9) | 0 | 1 (0.6) |
| Most common TEAEs occurring in >1 person overall | | | | |
| Medical device site reaction | 2 (3.7) | 0 | 3 (5.6) | 5 (3.1) |
| Dysmenorrhea | 1 (1.9) | 3 (5.6) | 1 (1.9) | 5 (3.1) |
| Dizziness | 1 (1.9) | 0 | 3 (5.6) | 4 (2.5) |
| Nausea | 1 (1.9) | 0 | 2 (3.7) | 3 (1.9) |
| Arthralgia | 0 | 1 (1.9) | 1 (1.9) | 2 (1.2) |
| Headache | 0 | 1 (1.9) | 1 (1.9) | 2 (1.2) |
| Rash | 0 | 1 (1.9) | 1 (1.9) | 2 (1.2) |

Abbreviation: TEAE, treatment-emergent adverse event.

where AUC exposures are twofold greater in subjects with impaired renal function than in subjects with normal renal function. However, steady-state bempedoic acid $C_{max}$ in subjects with renal impairment are increased by 1.0- to 1.4-fold relative to subjects with normal renal function and these changes are not considered to be clinically meaningful. Thus, bempedoic acid PK at a dose of 240 mg represents the upper range of exposure levels expected in standard clinical practice.

Bempedoic acid was characterized by a weak interaction at the hERG potassium channel in vitro. A comparison of hERG $IC_{50}$ (>1000 μM) and steady-state unbound bempedoic acid $C_{max}$ at the therapeutic dose of 180 mg/day (0.599 μM) indicated a safety margin of greater than 1670-fold. In monkeys, bempedoic acid doses up to 100 mg/kg did not produce significant changes in any of the measured cardiovascular parameters, including QT interval. Although toxicokinetic sampling was not conducted in the monkey cardiovascular safety study, mean estimates of $C_{max}$ and AUC exposures from a 1-month good laboratory practice toxicology study in monkeys following bempedoic acid 60 mg were 216 μg/ml and 1970 μg·h/ml, respectively (unpublished data); and these data were extrapolated to provide $C_{max}$ estimates after 100-mg/kg dosing. An in vivo safety margin of ~ 17.5-fold is predicted from a comparison of the estimate of $C_{max}$ (360 μg/ml, adjusted to a 100-mg/kg dose of bempedoic acid) in monkeys and corresponding human steady-state bempedoic acid $C_{max}$ (20.6 μg/ml) at the approved daily clinical dose of 180 mg.[7] The corresponding ratio of unbound bempedoic acid $C_{max}$ (18 μg/ml; 5% unbound) in monkeys and humans (0.206 μg/ml; 1% unbound) indicates an 87-fold greater unbound concentration in monkeys. Although ESP15228 was not directly assessed in the hERG assay or in the safety pharmacology study, previous PKs in monkeys indicated the ratio of ESP15228 to bempedoic acid was similar to that in humans (~ 15%) and estimates of $C_{max}$ in monkeys after 60 mg/kg dosing exceeded the clinical human steady-state $C_{max}$ by a factor of 12. These comparisons of human steady-state $C_{max}$ exposures and estimates of nonclinical exposures predict a low probability of QT/QTc interval prolongation in human subjects who receive bempedoic acid.

In the phase I clinical study, bempedoic acid 240 mg was generally well-tolerated without adverse safety signals and was not associated with clinically significant change in QT/QTc intervals or other cardiovascular parameters. Bempedoic acid 240 mg resulted in a mean estimate of $C_{max}$ of 30.4 μg/ml on day 9, ~ 1.5-fold greater than $C_{max}$ at steady-state (20.6 μg/ml) following administration of the approved 180 mg dose, with a predicted ddQTcF of 0.947 msec. A plasma concentration of 45 μg/ml was the highest achieved across all study subjects after 240-mg dose administration, ~ 2.2-fold greater than $C_{max}$ at steady-state at the 180-mg dose level, and had a predicted ddQTcF of 1.789 msec (Figure 3). Additionally, the impact of ESP15228 was directly assessed in humans, as the measured effect on the QT interval accounts for both bempedoic acid and its active metabolite at levels that likely exceeded human exposures at the therapeutic dose. Thus, in the event of a positive effect on QTc from supratherapeutic bempedoic acid dosing, the risk of QTc prolongation at lower doses could be estimated using concentration-QT analysis.

For both bempedoic acid and ESP15228, the upper confidence boundaries of ddQTcF were consistently below 10 msec and the corresponding slopes were not significantly different from zero, based on the 90% CI estimates (Figure 3). For bempedoic acid, the predicted mean change (90% CI) in QTcF at the observed mean steady-state concentration at 2 h postdose was −0.5 msec (−5.0, 4.0 msec; Table 2), approximating the median time to maximum steady-state concentration of bempedoic acid of 2.1 h (Table 3). In addition, latent changes in QTc intervals were not observed after the time of maximum bempedoic acid concentrations (Figure 1), consistent with a lack of QTc effects due to ESP15228 or bempedoic acid–glucuronide metabolite exposures. Inclusion of the moxifloxacin-positive control confirmed that the study was adequately sensitive to detect an effect on QTc, as the lower bounds of the 90% CI exceeded 5 msec at 2 and 4 h after dosing in the mixed-effects model for this group.

Limitations of the clinical study included its short duration and specific shortcomings in the experimental approach. Although bempedoic acid is indicated for long-term use, steady-state levels of bempedoic acid and its active metabolite were achieved after 9 days of dosing and are representative of plasma concentrations in patients receiving long-term treatment. In addition, the current analysis of concentration-QTcF did not consider a prespecified linear mixed-effects model to exclude a 10-msec QTc prolongation effect as recommended in a recent white paper.[14] The current model structure did not include a baseline influence of treatment on intercept and did not control for bias due to subjectivity in model selection. The absence of diurnal variation and hysteresis between bempedoic acid PKs and QTcF were also not confirmed in the analysis. However, pronounced increases in the ddQTcF effect were not observed at the time of maximum ESP15228 concentration (Figure 1). The potential effects of hysteresis and diurnal variation are unlikely to have influenced parameter estimates of the current model such that a different interpretation of cardiac safety would have resulted, given the previous knowledge of the disposition of each analyte, that all measurements were collected at approximately the same time each day, and a placebo arm was included in the study. Finally, the clinical study was conducted in healthy subjects and does not account for potential comorbidities in patients with hypercholesterolemia. However, the lack

of related clinical issues in phase III clinical trials of bempedoic acid[8–11,15] suggest that these results translate to populations of patients who would typically be prescribed long-term bempedoic acid.

## CONCLUSION

Steady-state bempedoic acid at a supratherapeutic dose of 240 mg was generally well-tolerated and not associated with QTc prolongation in healthy subjects. These clinical findings were consistent with findings in nonclinical studies that demonstrated minimal in vitro inhibition of hERG activity up to bempedoic acid concentrations of 1000 μM and a lack of bempedoic acid-related changes in HR, blood pressure, or cardiac depolarization in cynomolgus monkeys at bempedoic acid doses up to 100 mg/kg.

### ACKNOWLEDGEMENTS

Medical writing support, funded by Esperion Therapeutics, Inc., was provided by Kelly M Cameron, PhD, CMPP™, of JB Ashtin, who developed the first draft based on an author-approved outline and assisted in implementing author revisions, and Lamara D. Shrode, PhD, CMPP™, who assisted in preparing the manuscript for submission.

### CONFLICT OF INTERESTS

All authors are current (B.M.A. and M.G.E.) or former (D.E.M.D., W.J.S., and C.T.C.) employees of Esperion Therapeutics, Inc. and may hold stock or stock options. W.J.S. is currently the Principle, Cardiometabolic Consulting, LLC. Medical writing support, funded by Esperion Therapeutics, Inc., was provided by JB Ashtin.

### AUTHOR CONTRIBUTIONS

B.M.A., C.T.C., D.E.M., W.J.S., and M.G.E. wrote the manuscript, designed the research, performed the research, and analyzed the data.

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### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Amore BM, Cramer CT, MacDougall DE, Sasiela WJ, Emery MG. Absence of effect of steady state bempedoic acid on cardiac repolarization: Results of a thorough QT/QTc study in healthy volunteers. *Clin Transl Sci*. 2021;14:2487–2496. https://doi.org/10.1111/cts.13116