CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211616Orig1s000

INTEGRATED REVIEW

Executive Summary
Interdisciplinary Assessment
Appendices

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number	211616
Priority or standard	Standard
Submit date	2/20/2019
Received date(s)	2/21/2019
PDUFA goal date	2/20/2020
Division/office	Division of Metabolism and Endocrinology Products (DMEP)
Review completion date	2/19/2020
Established/proper name	Bempedoic acid
(Proposed) proprietary name	Nexletol
Pharmacologic class	adenosine triphosphate-citrate lyase (ACL) inhibitor
Code name	ETC-1002
Applicant	Esperion Therapeutics, Inc.
Dosage form/formulation(s)	Tablets, 180 mg
Dosing regimen	One tablet daily
Applicant proposed indication(s)/population(s)	Adjunct to diet (b) (4) who require additional lowering of low-density lipoprotein cholesterol (LDL-C)
Proposed SNOMED indication	55822004 (hyperlipidemia)
Regulatory action	Approval
Approved indication(s)/ population(s) (if applicable)	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 LDL-C
Approved SNOMED term for indication	55822004 (hyperlipidemia)

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Glossary

ACL	adenosine triphosphate-citrate lyase
ACSLV1	very long chain acyl-Coenzyme A synthetase 1
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMPK	adenosine monophosphate-activated protein kinase
ANCOVA	analysis of covariance
Apo	Apolipoprotein
Apo-B	Apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	bioavailability
BCRP	breast cancer resistance protein
BL	baseline
BLA	biologics license application
BMI	body mass index
BPH	benign prostatic hyperplasia
BUN	blood urea nitrogen
CDER	Center for Drug Evaluation and Research
CETP	cholesterylester transfer protein
CFR	Code of Federal Regulations
CI	confidence interval
CION-01	heptanoic acid 2,2-dimethyl-7-chloro-ethyl ester
CION-02	heptanoic acid, 2,2-dimethyl-7-iodo-ethyl ester
C_{max}	maximum plasma concentration
CL/F	steady-state clearance
CoA	coenzyme A
COD	cause of death
Cr	creatinine
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
DDI	drug-drug interaction
DPMH	Division of Pediatric and Maternal Health
ECG	electrocardiogram
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EOP2	end-of-phase 2
FDA	Food and Drug Administration
FFA	free fatty acids

FPG	fasting plasma glucose
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
Hct	hematocrit
HD	high dose
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HFHC	high-fat, high-cholesterol containing diet
Hgb	hemoglobin
HMG	3-hydroxy-3-methylglutaryl
hsCRP	high-sensitivity C-reactive protein
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IND	investigational new drug
ISS	integrated summary of safety
ITT	intention-to-treat
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LLN	lower limit of normal
LMT	lipid-modifying therapy
LOCF	last observation carried forward
LS	least squares
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intention-to-treat
MOA	mechanism of action
MRHD	maximum recommended human dose
MTD	maximum tolerated dose
NDA	new drug application
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PCSK9	proprotein convertase subtilisin/kexin type 9
P-gp	P-glycoprotein
PK	pharmacokinetics
PMR	postmarketing requirement
PPAR	peroxisome proliferator activated receptor
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation

TBM	to-be-marketed
TEAE	treatment-emergent adverse event
TG	triglycerides
T_{max}	time to maximum concentration
TK	toxicokinetic
TQT	thorough QT
ULN	upper limit of normal
WBC	white blood cell

I. Executive Summary

1. Summary of Regulatory Action

The benefit-risk analysis for bempedoic acid is favorable for an indication as an adjunct to maximally tolerated statin therapy (b) (4) with established cardiovascular disease (CVD) or heterozygous familial hypercholesterolemia (HeFH) who require additional low-density lipoprotein cholesterol (LDL-C) lowering. The data support approval for these conditions of use. All review disciplines support approval.

The two pivotal trials in the intended population (Trials 040 and 047) achieved the primary endpoint. Bempedoic acid lowered LDL-C in high-risk patients on a background of maximally tolerated statin who required additional LDL-C lowering. About 91% of patients were on either moderate- or high-intensity statin therapy at baseline in the two trials.

Bempedoic acid represents an additional therapeutic option in high-risk patients unable to meet goals with standard therapy (maximally tolerated statin, with or without ezetimibe or a PCSK9 inhibitor), despite its modest treatment effect on LDL-C (17% to 18% placebo-adjusted decrease from baseline at 12 weeks) in this context. Elevated cholesterol is an established risk factor for cardiovascular (CV) disease. Lowering LDL-C in several clinical trials with HMG-CoA reductase inhibitors (statins) and with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has demonstrated reduced CV risk. LDL-C is an accepted surrogate for drug approval if the overall benefit-risk calculus of the investigational product is favorable.

(b) (4)

(b) (4)

Review of safety data identified multiple issues, but these findings—either individually or collectively—do not outweigh efficacy in the intended population.

Bempedoic acid use was associated with an increased risk of tendon rupture. In the pooled 1-year clinical trials, 0.5% of patients treated with bempedoic acid experienced tendon rupture compared to no cases in placebo-treated patients. The risk can be adequately addressed in labeling, given the overall low incidence and identification of potential risk factors, such as concomitant use of fluoroquinolones and previous tendon injury.

More bempedoic acid–treated patients developed increases in uric acid compared to placebo-treated patients, a finding consistent with known bempedoic acid inhibition of the renal tubular transporter Organic Anion Transporter 2 (OAT2). In addition to the laboratory abnormality, there was also an increase in gout adverse events with bempedoic acid compared to placebo. Patients with a previous history of gout were at highest risk for a new event in the clinical trials. Increases in uric acid and increased incidence of gout events can be adequately mitigated via labeling, including a recommendation to monitor uric acid levels when clinically indicated.

There was an imbalance in benign prostatic hypertrophy adverse events in men treated with bempedoic acid compared to placebo. The risk may be adequately communicated in labeling.

More bempedoic acid–treated patients experienced decreases in total white blood cell (WBC) and neutrophils than placebo-treated patients. In clinical trials, there was a small increase in skin or soft tissue infections in the bempedoic arm, but there was no imbalance in other infections. The risk of decreased WBC (b) (4) can be adequately mitigated via labeling.

More bempedoic acid–treated patients experienced increases in creatinine, increases in blood urea nitrogen (BUN), and decreases in estimated glomerular filtration rate (eGFR) than placebo-treated patients. Changes in renal lab parameters are most likely related to OAT2 inhibition by bempedoic acid and were reversible following drug discontinuation.

Bempedoic acid was associated with imbalances in several other laboratory parameters without apparent clinical consequences. These changes can be adequately communicated in labeling. More bempedoic acid–treated patients experienced decreases in hemoglobin than placebo-treated patients. More bempedoic acid–treated patients experienced increases in platelet counts compared to placebo-treated patients. More bempedoic acid–treated patients experienced decreases in alkaline phosphatase than placebo-treated patients.

The observed imbalance in all-cause mortality between treatment arms in the two 1-year trials in high CV-risk patients (Trials 040 and 047) is likely a chance finding. The absolute imbalance is

small, considering 2:1 randomization. There were 25 (1.2%) deaths among 2009 patients assigned to bempedoic acid compared to 8 (0.8%) deaths among 999 placebo patients, or 25 observed versus 16 expected in the bempedoic acid arm.

The greatest imbalance was in cancer deaths, 9 (0.4%) in the bempedoic acid group versus one (0.1%) in placebo (9 observed versus 2 expected). Despite an observed imbalance in cancer deaths, there was no imbalance between arms in cancer diagnoses. Most cancer deaths occurred in patients with less than 30 days of drug exposure diagnosed with cancer within 6 months of randomization, inconsistent with a causal association, when accounting for latency.

The difference in CV deaths was small, 12 (0.6%) in the bempedoic acid arm versus 5 (0.5%) in placebo (12 observed versus 10 expected). An imbalance favoring placebo (higher rate of events in bempedoic acid arm) occurred in only one of the two pivotal trials and was not supported by an overall imbalance in nonfatal CV events, as there were higher rates of three-component major adverse cardiovascular event (MACE) events and 5-point MACE events in the placebo arm.

The nonclinical reviewer supports approval. Mortality secondary to hypoglycemia in rats and monkeys and lactic acidosis in rats were observed with bempedoic acid monotherapy at relatively high multiples of clinical exposure. Other findings of concern included liver toxicity and anemia in rodents, and potential renal effects (increases in creatinine and BUN) in monkeys. Synergistic toxicologic interactions occurred between bempedoic acid and atorvastatin resulting in deaths, hypoglycemia and atorvastatin-related liver toxicity in monkeys at lower bempedoic acid doses when given in combination with atorvastatin compared to the toxic doses when bempedoic acid or atorvastatin were administered to monkeys alone. Follow-up studies established that significant toxicity with the combination did not occur at clinically relevant exposures for either component, and hypoglycemia is monitorable and reversible. The type of liver toxicity observed in rodents is considered unlikely to be relevant to humans, because the effects in rodents were due to PPAR agonism and rodents are established to be hypersensitive compared to humans. Reduced red blood cell mass and changes in renal parameters have been observed clinically and are monitorable.

A nonclinical carcinogenicity study in rats demonstrated increased risk in the combined incidence of pancreatic islet cell adenomas and carcinomas in males at systemic exposures that approximate the clinical exposure at the human dose of 180 mg. The clinical relevance of this finding is unclear. These findings will be included in labeling.

The clinical pharmacology reviewer supports approval. Dose-response studies demonstrated maximal LDL-C lowering at 180 mg daily, with no additional efficacy at the higher dose of 240 mg and lesser efficacy at 120 mg daily. Dose-related safety findings (changes in uric acid, creatinine, BUN, and hemoglobin) reached plateau at 80 mg daily, with no potential to reduce the risk in comparison to 180 mg daily.

Bempedoic acid increases systemic exposure of several statins or their active metabolites when coadministered, but only two require dose limitation to avoid toxicity. Prescribers should avoid concomitant use of bempedoic acid in patients taking simvastatin greater than 20 mg daily or in patients taking pravastatin greater than 40 mg. Dose adjustment of statins is not recommended to allow use of bempedoic acid, given the known clinical benefits and extensive safety record of the former.

The Office of Pharmaceutical Quality (OPQ) review team recommends approval. OPQ concluded that the bempedoic acid application meets all applicable standards to support the identity, strength, quality, and purity.

In summary, bempedoic acid demonstrates a modest, but clinically relevant, decrease in LDL-C when used as an adjunct to maximally tolerated statin therapy. The most serious risks identified in the development program are an increased risk of tendon rupture, hyperuricemia, and gout. The benefit-risk of this product is favorable as adjunctive therapy to maximally tolerated statins in patients at high-risk of CV events who require additional lowering of LDL-C. (b) (4)

[redacted]

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	Large burden of cardiovascular (CV) disease in United States: • 93 million U.S. adults (2018) • Leading cause of death in United States • $555 billion annual healthcare expense (2016) LDL-C reduction with statins and PCSK9 inhibitors is associated with improved CV outcomes: • Meta-analysis of statin trials demonstrated that an absolute reduction of 38.7 mg/dL (1 mmol/L) with statins is associated with a 22% relative risk reduction in 5-year incidence of major coronary events,[1] ischemic stroke, and revascularization • Outcomes trials of the two approved PCSK9 inhibitors demonstrated association between LDL-C lowering with these agents and reduced risk of CV events[2] LDL-C reduction with other agents is used in high-risk patients who require additional LDL-C lowering: • A single outcomes trial with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering • Other agents may be used as adjuncts to statins, PCSK9i, and ezetimibe, but the incremental effects on outcomes are uncertain Patients with elevated LDL-C are treated for primary and secondary prevention of CV events: • Primary prevention: Reduce the risk for development of CV disease in patients at increased risk • Secondary prevention: Reduce the risk for additional CV events	LDL-C reduction with therapies targeting upregulation of the LDL-C receptor is a cornerstone of preventive treatment for CV disease. Reduction in LDL-C with statins and PCSK9 inhibitors is associated with decreased CV risk in in clinical trials of LDL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	Treatment options Monotherapy • Statins (-28% to -60% LDL-C reduction) – High-intensity statin, ≥50% reduction – Moderate-intensity statin, 30% to 49% reduction – Low-intensity statin, <30% reduction • Ezetimibe (-18% to -20% reduction) Add-on therapy • Statin+ezetimibe (-13% to -20% additional lowering) • Statin+PCSK9 inhibitors (PCSK9i) (-47% to -63% additional lowering) Treatment recommendations, 2018 ACC/AHA Guidelines • Primary prevention – Moderate-intensity statin to reduce LDL-C by 30% to ≥50% depending on calculated CV risk • Secondary prevention, not very high-risk for recurrence* – High-intensity statin to reduce LDL-C by ≥50% +/- ezetimibe • Secondary prevention, very high-risk for recurrence* – High-intensity statin to reduce LDL-C <70 mg/dL + ezetimibe +/- PCSK9i Patient access to newer add-on therapies, such as PCSK9 inhibitors, has been challenging due to factors such as expense and refusal of payers to cover.	Current treatment guidelines for LDL-C reduction are based on an individualized approach which considers a patient's overall risk for a CV event, specifically established ASCVD and additional risk factors. Moderate- or high-intensity statins are considered first-line therapy for all patients who require LDL-C reduction, depending on risk category. Low-intensity statins are not recommended for any population. Ezetimibe and/or PCSK9i are considered as second-line, add-on drugs to a background of maximally tolerated statin therapy in patients at highest CV risk who require additional LDL-C reduction. Statins reduce LDL-C by 30% to 60% depending on the statin intensity. PCSK9i lower LDL-C by an additional 50% to 60%. Ezetimibe lowers LDL-C by an additional 15% to 20%. Other drug categories, such as fibrates or niacin, are generally not considered mainstays of therapy due to mild LDL-lowering ability, limited efficacy, and absence of outcomes data as an adjunct to statins. Additional agents may be used in patients who require additional LDL-C lowering despite optimum therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	In patients with established ASCVD who take bempedoic acid for secondary prevention as add-on to background statin therapy, bempedoic acid lowers LDL compared to placebo: • At 12 weeks, -17.0% to -17.9% reduction • At 52 weeks, -11.3% to -12.5% reduction A cardiovascular outcomes trial to evaluate the benefit of bempedoic acid as an adjunct to statin therapy is ongoing.	Bempedoic acid has a relatively small treatment effect, compared to currently available therapies for LDL-C reduction. The treatment effect of bempedoic acid is similar to ezetimibe monotherapy or low-intensity statins, which are considered less effective interventions. In the absence of outcomes data, the clinical benefit is uncertain. Nonetheless, bempedoic acid may provide an additional option for patients who require LDL-C lowering despite optimized available therapies.
Risk and risk management	In phase 3 trials, bempedoic acid was associated with: • Tendon rupture (0.5% of patients) compared to placebo (0%) • Increased serum uric acid (3.5% versus 1.1% in placebo) and gout (1.5% versus 0.4% in placebo) • New-onset BPH in men (1.3% versus 0.1% in placebo) Bempedoic acid was also associated with changes across multiple lab parameters compared to placebo including decreased hemoglobin, decreased total WBC and neutrophils, increased platelets, increased BUN and creatinine, reduced eGFR, increased ALT/AST, increased CK, and decreased bone alkaline phosphatase: • Lab changes were generally small and reversible upon drug discontinuation • For patients with the greatest changes, no evidence of untoward clinical consequence	Bempedoic acid is associated with several serious safety signals of clinical significance, including tendon rupture, development of gout, nephrolithiasis, and new-onset BPH. However, these risks are low incidence, monitorable, and can be adequately addressed through labeling. Bempedoic acid is also associated with numerous changes to lab parameters. These changes are generally amenable to physician monitoring, reversible upon drug discontinuation, and did not require additional medical intervention in clinical trials.

[1] Baigent, et al. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010; 276: 1670-81.
[2] Sabatine, et al. NEJM 2017: 376: 1713-22; Schwartz, et al. NEJM 2018; 379: 2097-107.
*Very high-risk for recurrence includes patients with history of multiple major ASCVD events (MI, stroke, PAD, or recent ACS); or one major ASCVD event plus multiple high-risk conditions (age ≥65, HeFH, DM, HTN, CKD, current smoker, LDL-C ≥100 mg/dL despite maximal therapy, or history of CHF/CABG/PCI)
Abbreviations: ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BPH, benign prostatic hyperplasia; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CHF, congestive heart failure; CK, creatine kinase; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HeFH, heterozygous familial hypercholesterolemia; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; WBC, white blood cell

Conclusions Regarding Benefit-Risk

Limited options exist for second-line, add-on therapy medications for patients at risk for CV events who have maximized their statin dose yet require additional LDL-C reduction. Approval of bempedoic acid would provide an additional option to lower LDL-C in these patients. The treatment effect of bempedoic acid is small compared to statins (moderate intensity or higher) or PCSK9 inhibitors, and comparable to ezetimibe, and evaluation of its potential effect on the risk of CV events is ongoing. The risks associated with therapy, notably tendon rupture and gout, may result in significant morbidity. Although numerous, laboratory abnormalities associated with bempedoic acid (hemoglobin, WBC, BUN, creatinine) do not appear to be of clinical significance. Although uncertain, the incidence of these risks does not appear to increase with prolonged treatment exposure. In high-risk patients, the presumed benefits of additional LDL-C lowering outweigh the potential risk, although appropriate patient selection will be an important factor. Overall, in the intended population, the benefit of bempedoic acid therapy appears to outweigh any risk associated with taking the drug. Completion of the ongoing CVOT will help clarify the benefit risk in certain other contexts. (b) (4)

II. Interdisciplinary Assessment

3. Introduction

The Applicant, Esperion Therapeutics, Inc., submitted this New Drug Application (NDA) in support of the following proposed indication:

> *NEXLETOL is an ACL inhibitor indicated as an adjunct to diet* (b) (4) [redacted] *Limitations of Use: The effect of NEXLETOL on cardiovascular morbidity and mortality has not been determined.*

Bempedoic acid is an inhibitor of adenosine triphosphate-citrate lyase (ACL), an enzyme in the cholesterol and fatty acid biosynthesis pathways. Bempedoic acid is administered orally once daily as 180 mg tablets.

Patients with elevated LDL-C are treated to reduce the risk of developing CV disease (primary prevention) or to reduce the risk of additional events in patients with established CV disease (secondary prevention). The 2018 AHA/ACC treatment guidelines for LDL-C reduction emphasize an individualized treatment approach to LDL-C reduction based on a patient's CV risk category (primary versus secondary prevention) and calculated predicted risk for future CV events. Statins are considered first-line therapy for all patients who require LDL-C reduction, regardless of CV risk category. Ezetimibe and PCSK9 inhibitors are recommended as second-line treatment options as add-on therapy to a background of optimized statin in patients at highest CV risk who require additional LDL-C reduction. Large outcome trials conducted over 3 decades have demonstrated the benefits of statins to reduce the risk of CV events in various populations. More recently, PCSK9 inhibitors have demonstrated reduced risk of CV events in patients with established CVD on maximally tolerated statins. Ezetimibe demonstrated a small but statistically significant reduction in CV events in a single outcomes trial. Other approved treatment options include fenofibrates and niacin; however, these drug classes are not considered mainstays of therapy due to limited efficacy on LDL-C and absence of data demonstrating an effect on CV events as an adjunct to statin therapy.

Bempedoic acid is a new molecular entity and is not currently marketed in the United States. The Applicant submitted investigational new drug (IND) 106654 in October 2009. During an end-of-phase 2 (EOP2) meeting in August 2015 and during a Type C Advice Meeting in May 2016, the U.S. Food and Drug Administration (FDA) advised the company that (b) (4) [redacted]

Review issues relating to the evaluation of benefit include:

Review issues relating to risk and risk management include:

- Death imbalance in phase 3 trials
    - CV death
    - Malignancy-associated death
- Safety evaluation
    - Tendon rupture
    - Increases in serum uric acid and gout
    - New-onset benign prostatic hyperplasia (BPH)
    - Changes to laboratory tests
        - Hematology: decreased hemoglobin and total WBC, increased platelets from baseline
        - Renal: increased BUN and creatinine, decreased eGFR
- Imbalance in pancreatic neuroendocrine adenoma and carcinoma in 2-year nonclinical carcinogenicity study
- Drug-drug interaction with statins

3.1. Approach to Review

The Applicant's phase 3 clinical development program consisted of two 52-week trials in high CV risk patients on maximally tolerated statins who required additional LDL-C lowering for secondary prevention (Trials 1002-040 and 1002-047). It also consisted of two short-term trials in primary hyperlipidemia patients on zero to low-dose statin who required LDL-C lowering for primary or secondary prevention (Trials 1002-046 and 1002-048), an open-label extension (OLE) trial that rolled over patients from Trial 1002-040 (1002-050), and an ongoing CVOT in high CV risk patients (b) (4) (Trial 1002-043).

Based on the Division's previous advice to the Applicant, this review focused on Trials 040 and 047 (subsequently referred to as "high CV risk" trials), (b) (4) Supportive efficacy and safety data come from Trials 046 and 048 (subsequently referred to as "no/low statin" trials) and the OLE trial.

No data from the ongoing CVOT were submitted to the NDA. The CVOT is a randomized, double-blind, placebo-controlled, parallel group, multi-center efficacy and safety study in approximately 14,000 adult patients (randomized 1:1 to bempedoic acid and placebo) with, or at high risk for, cardiovascular disease who are "statin intolerant". The study is designed to assess the effects of bempedoic acid on the occurrence of major cardiovascular events (b) (4) The CVOT is fully enrolled, follow-up is ongoing, and the current anticipated completion date is October 2022.

Table 3. Clinical Trials in Support of Efficacy and/or Safety Determinations[1] for Bempedoic Acid

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned/Actual Randomized[2]	Number of Centers and Countries
1002-040	Secondary prevention: High CV risk (ASCVD and/or HeFH) on maximally tolerated statin who require additional LDL-C lowering	Control type: Placebo-controlled Randomization: 2:1, stratified by HeFH status and baseline statin intensity Blinding: Double-blind Biomarkers: LDL-C	Drug: Bempedoic acid Dose: 180 mg Number treated: 1,488 Duration (quantity and units): 52 wk Drug: Placebo Number treated: 742 Duration (quantity and units): 52 wk	Primary: percent change from baseline to Week 12 in LDL-C Secondary: percent change from baseline to Week 24 in LDL-C; percent change from baseline to Week 12 in non-HDL-C/TC/Apo-B/hsCRP	1950/2230	114 centers in 6 countries
1002-047	Secondary prevention: High CV risk (ASCVD and/or HeFH) on maximally tolerated statin who require additional LDL-C lowering	Control type: Placebo-controlled Randomization: 2:1, stratified by HeFH status and baseline statin intensity Blinding: Double-blind Biomarkers: LDL-C	Drug: Bempedoic acid Dose: 180 mg Number treated: 522 Duration (quantity and units): 52 wk Drug: Placebo Number treated: 257 Duration (quantity and units): 52 wk	Primary: percent change from baseline to Week 12 in LDL-C Secondary: percent change from baseline to Week 24 in LDL-C; percent change from baseline to Week 12 in non-HDL-C/TC/Apo-B/hsCRP; absolute change from baseline to Weeks 12 and 24 in LDL-C	750/779	86 centers in 6 countries

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned/Actual Randomized[2]	Number of Centers and Countries
1002-046	Primary and secondary prevention: Patients with hyperlipidemia on zero to very-low-dose statin	Control type: Placebo-controlled Randomization: 2:1, stratified by primary versus secondary prevention Blinding: Double-blind Biomarkers: LDL-C	Drug: Bempedoic acid Dose: 180 mg Number treated: 234 Duration (quantity and units): 24 wk Drug: Placebo Number treated: 111 Duration (quantity and units): 24 wk	Primary: percent change from baseline to Week 12 in LDL-C Secondary: percent change from baseline to Week 24 in LDL-C; percent change from baseline to Week 12 in non-HDL-C/TC/Apo-B/hsCRP; absolute change from baseline to Weeks 12 and 24 in LDL-C	300/345	64 centers in 2 countries
1002-048	Primary and secondary prevention: Patients with hyperlipidemia on zero to low-dose statin and ezetimibe	Control type: Placebo-controlled Randomization: 2:1 Blinding: Double-blind Biomarkers: LDL-C	Drug: Bempedoic acid Dose: 180 mg Number treated: 181 Duration (quantity and units): 12 wk Drug: Placebo Number treated: 88 Duration (quantity and units): 12 wk	Primary: percent change from baseline to Week 12 in LDL-C Secondary: percent change from baseline to Week 24 in LDL-C; percent change from baseline to Week 12 in non-HDL-C/TC/Apo-B/hsCRP	225/269	58 centers in 6 countries

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned/Actual Randomized[2]	Number of Centers and Countries
1002-050	High CV risk (ASCVD and/or HeFH) with hyperlipidemia	Control type: Open-label Blinding: N/A Biomarkers: LDL-C Innovative design features: Rollover from Trial 040	Drug: Bempedoic acid Dose: 180 mg Number treated: 1,462 Duration (quantity and units): 82 wk	Primary: treatment-emergent adverse events Secondary: absolute change from baseline in LDL-C at Weeks 52 and 78; percent change from baseline in LDL-C/non-HDL-C/TC/Apo-B/hsCRP/TG/HDL-C at Weeks 52 and 78	1300/1462	112 centers in 6 countries

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: Apo-B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable; TC, total cholesterol

4. Patient Experience Data

No patient experience data were submitted with this application.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data was submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

A high-level summary of clinical pharmacology information is shown in Table 5.

Table 5. General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Adenosine triphosphate-citrate lyase (ACL) inhibitor
Mechanism of action	Bempedoic acid is an ACL inhibitor that lowers low density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver. ACL is an enzyme upstream of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol (and fatty acid) biosynthesis pathway(s). Bempedoic acid and its active metabolite, ESP15228, require coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA and ESP15228-CoA, respectively. ACSVL1 is expressed primarily in the liver. Inhibition of ACL by ETC 1002 CoA and ESP15228-CoA results in decreased cholesterol synthesis in the liver and lowers LDL-C in blood via upregulation of low-density lipoprotein receptors.
Active moieties	Bempedoic acid-CoA, ESP15228-CoA
QT prolongation	In a randomized, double-blind, placebo- and positive-controlled, parallel-design thorough QT (TQT) study in healthy subjects, at a dose of 240 mg (1.3 times the approved recommended dose), bempedoic acid did not prolong the QT interval to any clinically relevant extent.
	General Information
Bioanalysis	Concentration of bempedoic acid, ETC-15228, and their glucuronide metabolites were quantified in plasma using LC-MS/MS method
Healthy subjects versus patients	PK is similar between healthy volunteers and patients
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Parameter — Mean ± SD AUC — 289 ± 96.4 µg·h/mL C_{max} — 20.6 ± 6.1 µg/mL C_{24} — 7.43 ± 3.18 µg/mL
Range of effective dose(s) or exposure	LDL-C lowering effect reached a maximum at 180 mg QD, with similar effect size at 240 mg QD
Maximally tolerated dose or exposure	Not identified. Doses up to 240 mg QD (highest dose tested in clinical trials) raised no major safety concerns.
Dose proportionality	Bempedoic acid steady-state pharmacokinetics were generally linear over a range of >60 mg to 220 mg.
Accumulation	The mean accumulation ratio was approximately 2.3-fold.
Time to achieve steady-state	About 120 hours

Characteristic	Drug Information
Bridge between to-be-marketed and clinical trial formulations	The to-be-marketed formulation (Tablet 2) was tested with other tablet formulations (Tablet 1 and Tablet 2A) in the pivotal phase 3 studies. However, food effect was evaluated only with Tablet 1 formulation but not with Tablet 2 formulation; relative bioavailability was evaluated only between Tablet 2A and Tablet 1 formulations. The difference between Tablet 2 and Tablet 2A formulations was considered minimal. See clinical pharmacology review section for details.
	Absorption
Bioavailability	Based on radio-labelled PK study, at least 70% of the administered dose was absorbed after oral administration. The absolute bioavailability was not determined in humans.
T_{max}	3.5 hours
Food effect (Fed/fasted) Geometric least square mean and 90% CI	The fed treatment (1×180-mg tablet) was given after the subjects had consumed a standardized FDA-defined, high-fat (approximately 50% of calories from fat), high-calorie (approximately 800-1,000 calories) breakfast. The breakfast derived approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat. Fed/Fasted Ratio (90% CI) $AUC_{0-\infty}$ 0.981 (0.931, 1.03) C_{max} 0.875 (0.787, 0.973) Food effect study was not evaluated with the to-be-marketed formulation. Concomitant food administration had no effect on the oral bioavailability of bempedoic acid when administered as an investigational tablet formulation.
	Distribution
Volume of distribution	The bempedoic acid apparent volume of distribution (V/F) was 18 L.
Plasma protein binding	Plasma protein binding of bempedoic acid, its glucuronide, and its active metabolite—ESP15228—were 99.3%, 98.8%, and 99.2%, respectively.
Drug as substrate of transporters	ETC-1002 and ESP15228 were not substrates for cellular transporters
	Elimination
Mass balance results	Following single oral administration of 240 mg of bempedoic acid (1.3 times the proposed recommended dose), approximately 70% of the total dose (bempedoic acid and its metabolites) was recovered in urine, primarily as the acyl glucuronide conjugate of bempedoic acid, and approximately 30% was recovered in feces. Less than 5% of the administered dose was excreted as unchanged bempedoic acid in feces and urine combined
Clearance	The steady-state clearance (CL/F) of bempedoic acid was 11.2 mL/min after once-daily dosing; renal clearance of unchanged bempedoic acid represented less than 2% of total clearance.
Half-life	The mean (SD) half-life for bempedoic acid in humans was 19 (10) hours at steady-state.
Metabolic pathway(s)	The primary route of elimination for bempedoic acid is through metabolism of the acyl glucuronide. Bempedoic acid is also reversibly converted to an active metabolite (ESP15228) based on aldo-keto reductase activity observed in vitro from human liver.
Primary excretion pathways (% dose)	(see mass balance results above)
	Intrinsic Factors and Specific Populations
Body weight	The pharmacokinetics of bempedoic acid were not affected by weight.
Age	The pharmacokinetics of bempedoic acid were not affected by age.

Characteristic	Drug Information
Renal impairment	The mean bempedoic acid AUC in subjects with mild renal impairment (n=8) were 1.5-fold higher compared to those with normal renal function (n=6). Relative to those with normal renal function, mean bempedoic acid AUCs were higher in patients with moderate (n=5) or severe (n=5) renal impairment by 2.3-fold and 2.4-fold, respectively.
Hepatic impairment	No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Bempedoic acid was not studied in patients with severe hepatic impairment (Child Pugh C).
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	In vitro metabolic interaction studies suggest that bempedoic acid, as well as its active metabolite and glucuronide forms, are not metabolized by and do not interact with cytochrome P450 enzymes.
Inhibition/induction of transporter systems	Bempedoic acid weakly inhibits OAT3 at high multiples of clinically relevant concentrations, and bempedoic acid and its glucuronide weakly inhibit OATP1B1, and OATP1B3 at clinically relevant concentrations. Bempedoic acid weakly inhibits OAT2 in vitro, which is likely the mechanism responsible for minor elevations in serum creatinine and uric acid
	Immunogenicity (for Biologics)
Bioanalysis	(Not applicable)
Incidence	(Not applicable)
Clinical impact	(Not applicable)

Abbreviations: CI, confidence interval; LC-MS/MS, liquid chromatography-tandem mass spectrometry; PK, pharmacokinetics; QD, once daily; SD, standard deviation

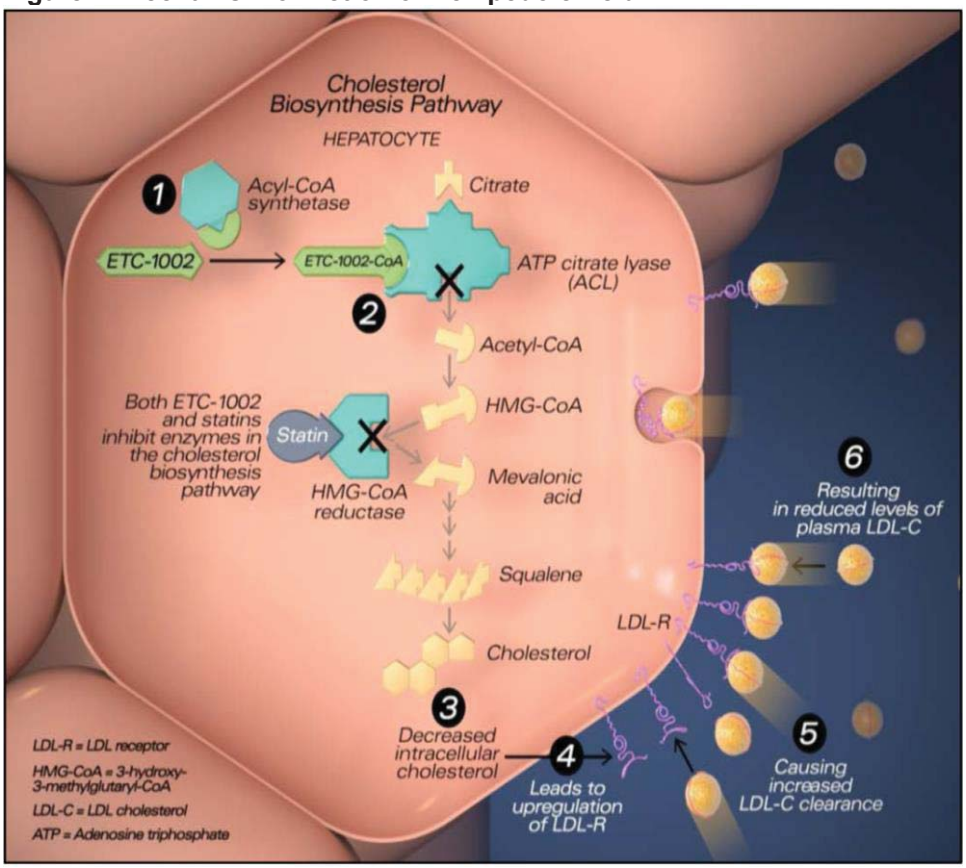
5.1. Nonclinical Assessment of Potential Effectiveness

Proposed Mechanism of Action

The potential effectiveness of bempedoic acid for the proposed indication was assessed in a series of nonclinical pharmacology studies designed to establish the mechanism of action and explore potential benefits. The findings from these studies support the following conclusions: ETC-1002 is a prodrug inhibitor of ACL, which is converted to its active form, ETC-1002-coenzyme A (CoA), by very long chain acyl-Coenzyme A synthetase 1 (ACSLV1) in the liver. ETC-1002-CoA mediates its effects through inhibiting ACL, a cytosolic enzyme upstream of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (the molecular target of statins), which catalyzes the cleavage of citrate into oxaloacetate and acetyl-CoA. Cytosolic acetyl-CoA serves as common substrate for de novo cholesterol and fatty acid synthesis. Thus, ACL inhibition leads to upregulation of low-density lipoprotein receptors (LDLRs) and increases clearance of plasma cholesterol in a manner similar to statins. Additional in vitro and in vivo studies support the potential efficacy of bempedoic acid for the treatment of hypercholesterolemia.

The summary of supporting evidence is described below, and details of the nonclinical pharmacology studies are provided in Section 13. The mechanism of action is shown in Figure 1.

Figure 1. Mechanism of Action of Bempedoic Acid



Source: Excerpted from Applicant's submission

In Vitro Activity Consistent With Proposed MOA

- In a cell-free system, ETC-1002-CoA, but not the parent molecule, directly inhibited recombinant human ACL in a concentration-dependent manner (K_i =2μM), while ETC-1002 was inactive.
- Bempedoic acid demonstrated potent inhibition of de novo lipid synthesis in vitro upon incubation with primary human hepatocytes with a mean half maximal inhibitory concentration (IC_{50}) of 9.7μM.
- In both primary human hepatocytes and RH7777 (rat hepatoma) cells, inhibition of lipid synthesis by bempedoic acid and genetic silencing of ACL led to a 50% upregulation of LDLR protein and a greater than 2-fold increase in LDLR activity. Bempedoic acid also induced a compensatory upregulation of key cholesterol-regulating genes including SREBP2, HMG-CoA reductase, and proprotein convertase subtilisin/kexin type 9 (PCSK9).

In Vivo Studies Supporting Proposed Indication

- In high fat, high cholesterol-containing diet (HFHC)-fed hamsters and Apo E-deficient mice, both accepted animal models of hyperlipidemia, treatment with bempedoic acid lowered plasma LDL-C by up to 38% and 60%, respectively.
- Bempedoic acid administration in dyslipidemic hamsters was also associated with reductions in other lipid parameters including hepatic triglycerides, cholesteryl esters, and free cholesterol.

Secondary (Off-Target) Pharmacology of Special Interest

- In vitro, both bempedoic acid and its active metabolite (ESP15288) weakly activated human PPARα (target of fibrates) and PPARγ (target of thiazolidinediones) at concentrations ≥100μM and showed biochemical and liver changes consistent with PPARα activation in rodent studies across all treatment durations and short-term monkey studies. In addition, bempedoic acid demonstrated the ability to activate adenosine monophosphate-activated protein kinase (AMPK) (indirectly activated by metformin) in both in vitro mechanistic and in vivo rodent studies. However, the weight of evidence and mechanistic studies excluded the involvement of PPAR and AMPK, respectively, in the bempedoic acid–mediated lowering of LDL-C in humans (refer to Section 13).

6. Evidence of Benefit (Assessment of Efficacy)

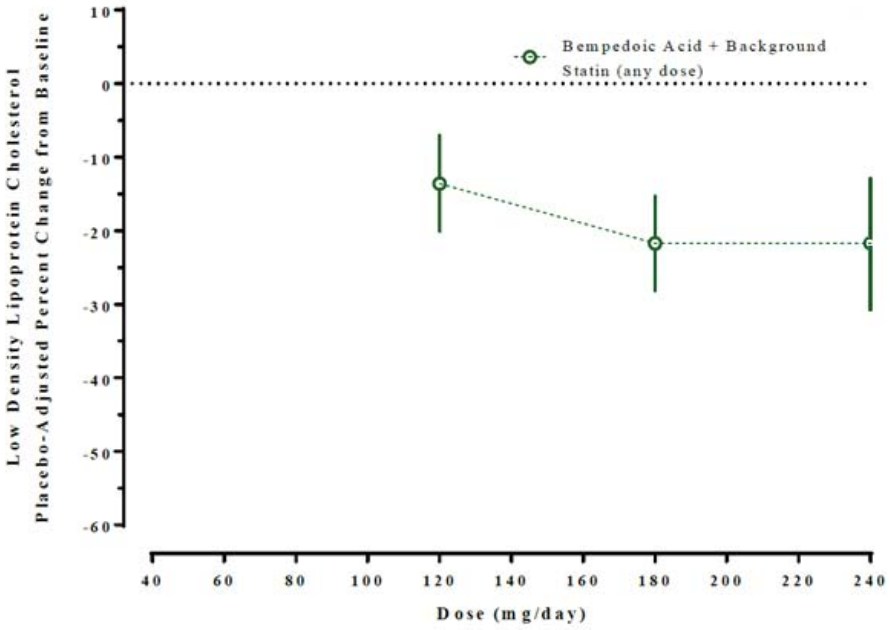
6.1. Assessment of Dose and Potential Effectiveness

The proposed dose selection of 180 mg once daily (QD) was based on six phase 2 dose-ranging studies in patients. A summary of the dose-response relationship is depicted in Figure 2 (with statins as background therapy) and Figure 3 (without any background therapy). When bempedoic acid was coadministered with statins as background therapy, a dose of 180 mg QD reached the maximum LDL-C lowering effect, with no additional efficacy gained at a higher dose of 240 mg QD. Lesser efficacy was observed at a lower dose of 120 mg QD. When bempedoic acid was coadministered with ezetimibe, the 180 mg QD dosing regimen similarly showed a better efficacy in LDL-C lowering effect in comparison to the 120 mg QD dosing regimen. (b) (4) Therefore, the dose selection of 180 mg QD is appropriate.

To be noted, in Figure 2, the trial evaluating bempedoic acid + background statins (any statin) had a corresponding comparative placebo control with statins as background therapy. In comparison (Figure 3), the trial evaluating bempedoic acid + ezetimibe 10 mg and bempedoic acid monotherapy had a corresponding comparative placebo control without any background therapy. The reader is cautioned against comparing the LDL-C lowering effect of bempedoic acid shown from the treatment of bempedoic acid + background statins (any statin) in Figure 2 with the other two treatments in Figure 3.

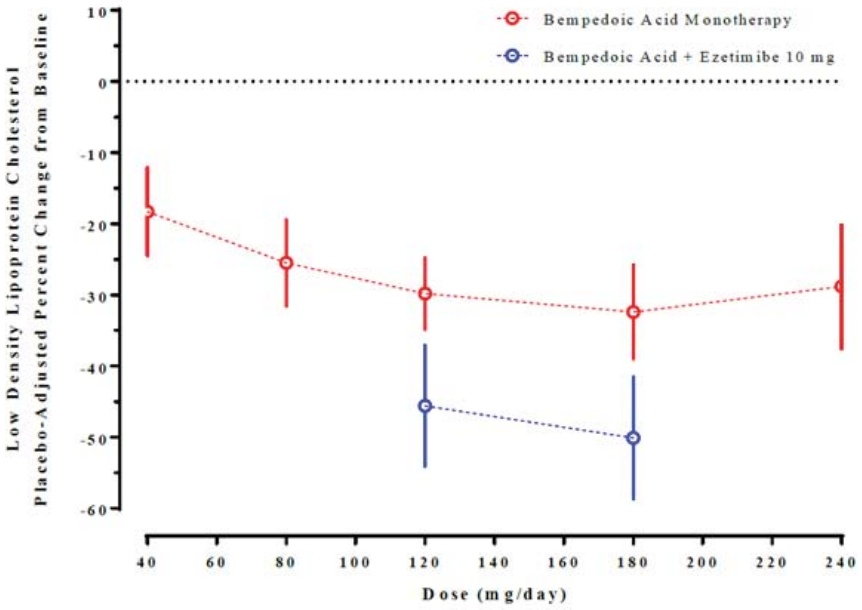
Detailed information about the phase 2 dose-response studies could be found in Section 14.2.1.

Figure 2. Placebo-Adjusted LS Mean Percent Change From Baseline by Daily Bempedoic Acid Dose Across Phase 2 Studies: Bempedoic Acid Coadministration With Statins (Study 007 and 009)



Source: Figure 10 in 2.7.2 Summary of Clinical Pharmacology Studies

Figure 3. Placebo-Adjusted LS Mean Percent Change From Baseline by Daily Bempedoic Acid Dose Across Phase 2 Studies: Bempedoic Acid Monotherapy (Pooled Data from Studies 003, 005, 006, and 008) and Co-administration With Ezetimibe (Study 008)

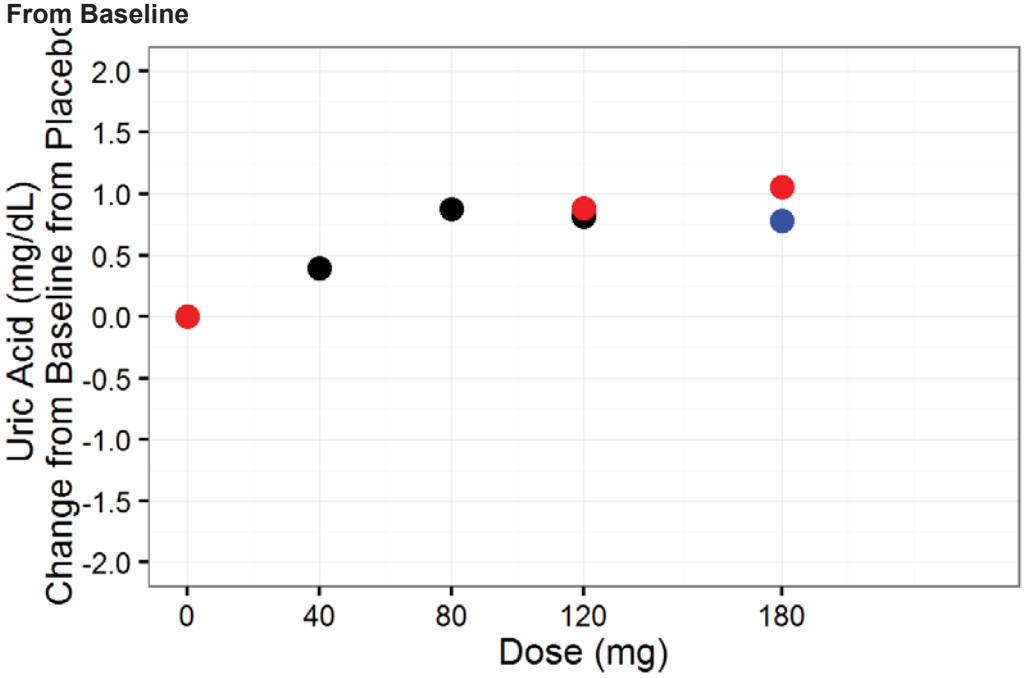


Source: Figure 10 in 2.7.2 Summary of Clinical Pharmacology Studies

Reviewer's Dose-Response Assessment for Safety

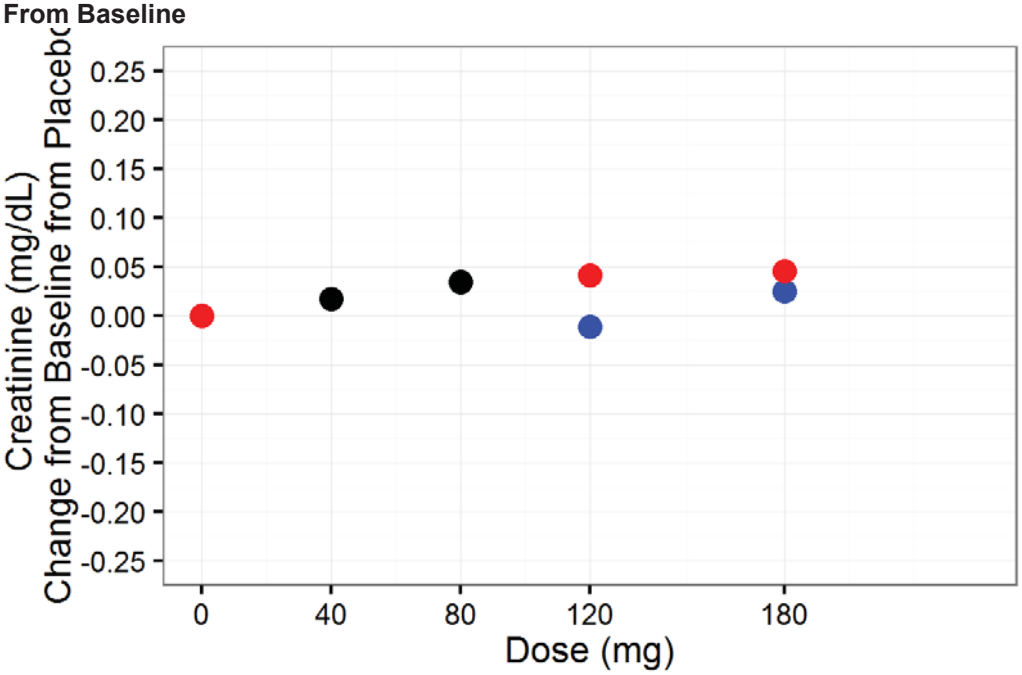
In the phase 3 clinical trials, higher rates of renal disorders, gout, and hemoglobin decrease were observed in the bempedoic acid 180 mg QD arms. As a result, dose-related changes in uric acid, Cr, BUN, and Hgb were evaluated retrospectively from Phase 2 dose ranging studies (Studies 003, 008, and 009) to inform dose selection based on these safety concerns. The corresponding dose-response evaluations for each endpoint at Week 12 are shown in Figure 4 to Figure 7. Based on these analyses, dose-related changes in uric acid, creatinine, BUN, and hemoglobin were observed up to 180 mg QD dosing of bempedoic acid and there was no appreciable increase in uric acid, creatinine, or BUN levels or decrease in hemoglobin between 80 and 180 mg QD dosing. Since maximal LDL-lowering was observed at the 180 mg QD dose and there was not a notable difference in these safety markers down to 80 mg QD, the proposed 180 mg QD is the optimal dosing regimen in the proposed patient population.

Figure 4. Dose-Response Relationship in Phase 2 Dose-Ranging Studies for Uric Acid Change From Baseline



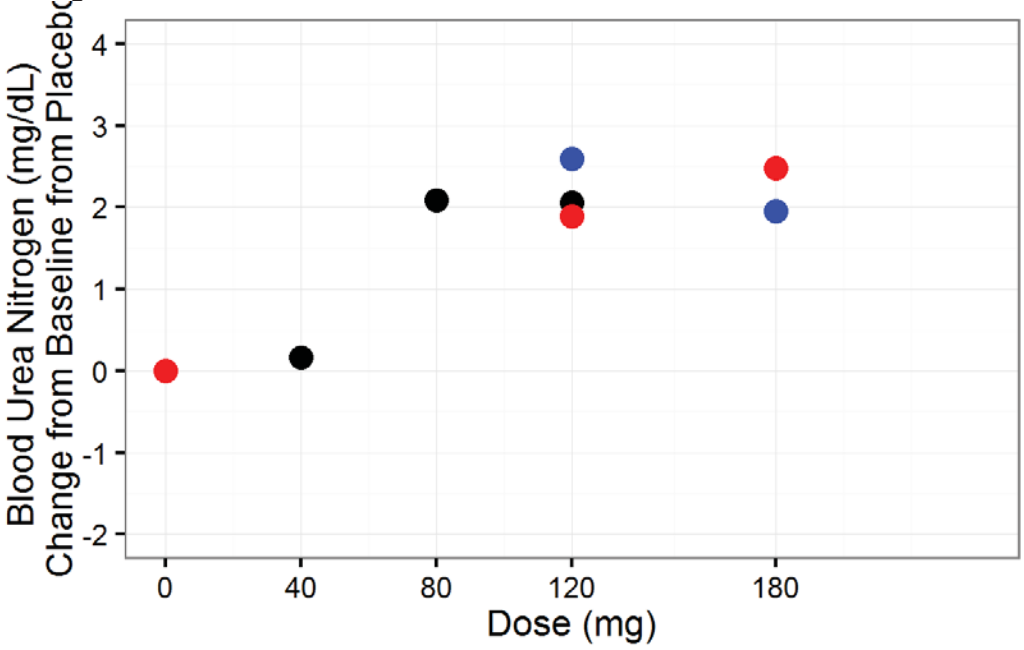
Source: Reviewer analysis
Red: Study 1002-003; Blue: Study 1002-008; Black: Study 1002-009

Figure 5. Dose-Response Relationship in Phase 2 Dose-Ranging Studies for Creatinine Change From Baseline



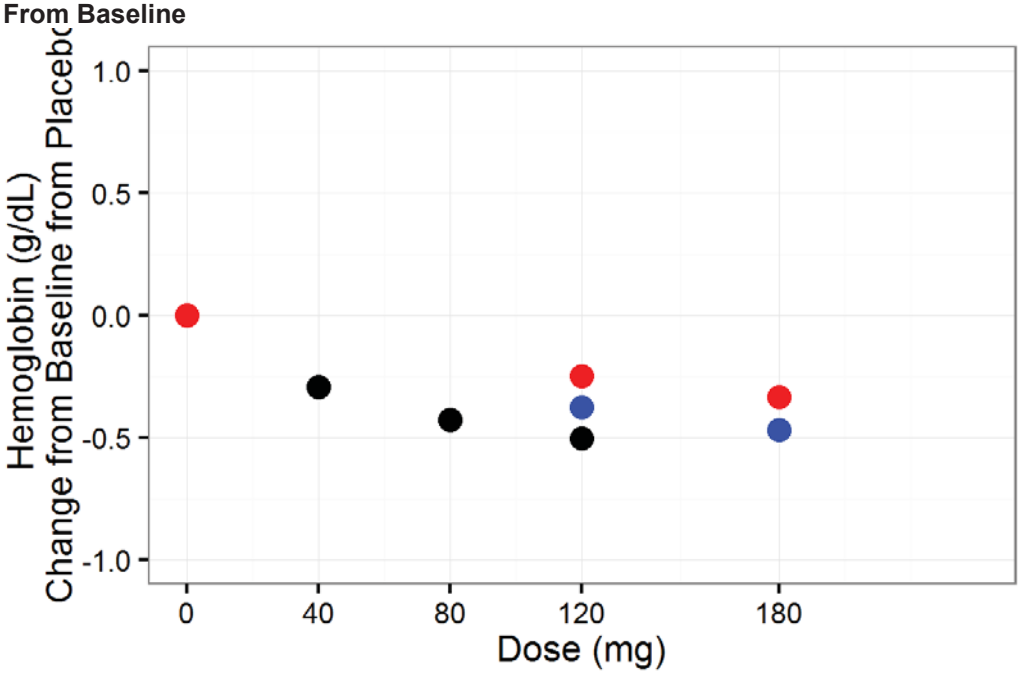
Source: Reviewer analysis
Red: Study 1002-003; Blue: Study 1002-008; Black: Study 1002-009

Figure 6. Dose-Response Relationship in Phase 2 Dose-Ranging Studies for Blood Urea Nitrogen Change From Baseline



Source: Reviewer analysis
Red: Study 1002-003; Blue: Study 1002-008; Black: Study 1002-009

Figure 7. Dose-Response Relationship in Phase 2 Dose-Ranging Studies for Hemoglobin Change From Baseline



Source: Reviewer analysis
Red: Study 1002-003; Blue: Study 1002-008; Black: Study 1002-009

Four different solid oral dosage formulations—capsule, tablet formulation 1, tablet formulation 2A, and tablet formulation 2—were used in the clinical development program. The three tablet formulations were used in the four pivotal phase 3 clinical trials. A distribution of the tablet formulations used in phase 3 clinical trials are shown in Table 6.

Table 6. Bempedoic Acid Formulations Used in Placebo-Controlled Phase 3 Clinical Studies

	Number of Subjects			Formulation			
		Randomized to					
Study	Total	Bempedoic Acid	Placebo	1 Only	2 Only	1 and 2	2A[a]
1002-040	2330	1488	742	475	0	1013	0
1002-046	345	234	111	33	160	41	0
1002-047	779	522	257	22	413	87	0
1002-048	269	181	88	76	62	0	43
Total	3723	2425	1198	606	635	1141	43
Overall percent	-	-	-	25%	26%	47%	2%

Source: Table 3 in 2.7.1 Summary of Biopharmaceutic Studies
Lot VVBX (bu k tablet lot number)/VWBX (package lot number).

For pharmacokinetics (PK) bridging purpose, the Applicant demonstrated bioequivalence between the capsule and tablet formulation 1 (Study 016) and between tablet formulation 1 and tablet formulation 2A (Study 036). Food effect on the rate and extent of absorption was evaluated using tablet formulation 1 only (Study 016). However, the to-be-marketed (TBM) formulation tablet formulation 2—which was used in some phase 3 pivotal clinical trials—has not been demonstrated to be bioequivalent to any other formulations. Food effect was not evaluated using this TBM formulation.

The Applicant provided the following evidence to support the PK bridging and food effect evaluation for the TBM formulation tablet formulation 2: physicochemical properties of bempedoic acid, formulation composition, in vitro release profiles, and population pharmacokinetic analysis.

The Applicant's classification of bempedoic acid as a BCS Class 2 compound was supported by its high permeability. The P_{app} (apparent permeability) of bempedoic acid using Caco-2 cell is 11.5×10-6 cm/sec, thus, bempedoic acid is classified as highly permeable.

Bempedoic acid is a weak acid (pKa 4.88 and 5.60) with high solubility under basic conditions. The pH dependent solubility profile is depicted in Figure 8. Bempedoic acid was insoluble below a pH of 5 when dissolved in aqueous media and becomes soluble at a pH of 5 and above.

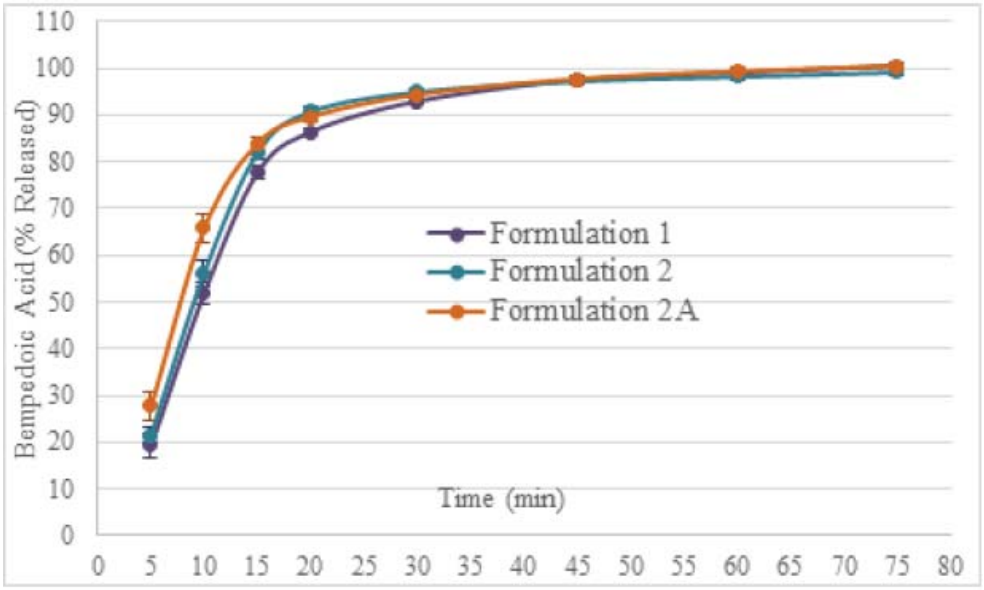
A summary of the formulation composition for the three different tablet formulations is given in Table 7, and the corresponding dissolution profiles are depicted in Figure 9. All three tablet formulations are immediate-release formulations. The only difference between tablet formulation 2A and formulation 2 is the (b) (4)
Similarity between formulations 1 and 2A and formulations 1 and 2 were evaluated using f_2 calculations performed using 4 points (5, 10, 15, and 20 minutes). The results demonstrate that dissolution is similar between formulations 1 and 2A (f_2=53) and between formulations 1 and 2 (f_2=70).

Table 7. Bempedoic Acid Formulation Composition

Component	Function	Weight (mg)			Percent of Total Weight			(b) (4)	
		Form 1	Form 2A	Form 2	Form 1	Form 2A	Form 2	Form 2A	Form 2
Core tablet									
Bempedoic acid	Active								
Microcrystalline cellulose[a]	(b) (4)								
Lactose									
Sodium starch glycolate									
Hydroxypropyl cellulose									
Magnesium stearate									
Colloidal silicon dioxide									
(b) (4)									
Core tablet weight									
Fill coating (b) (4)									
(b) (4)									
Total tablet weight (mg)									

Source: Table 4 in 2.7.1 Summary of Biopharmaceutic Studies
[a] Compendial excipient. Compendial testing includes conformance to USP, NF, Ph. Eur, and/or JP.
[b] (b) (4)
Abbreviations: Form, formulation; NA, not applicable; USP, United States Pharmacopeia

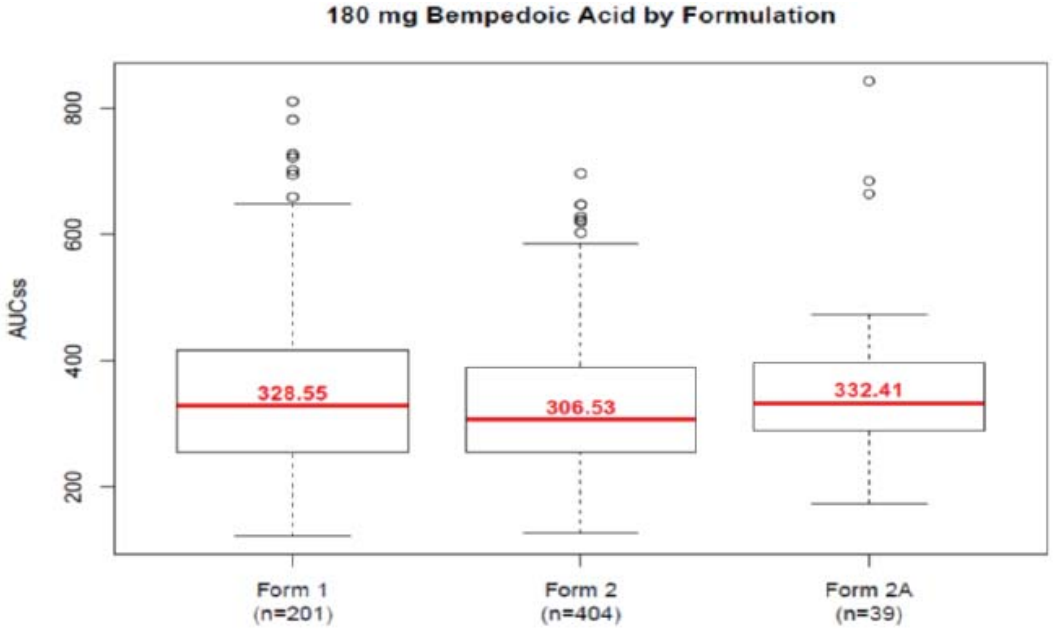
Figure 9. Dissolution Profiles for Formulations 1, 2A, and 2 in 900-mL Buffered Media, pH 6.6, Apparatus2 at 50 rpm



Source: Figure 6 in 2.7.1 Summary of Biopharmaceutic Studies

Given the minor difference in formulation composition and in vitro dissolution profiles between formulation 2A and formulation 2, no clinical meaningful difference between formulation 2A and formulation 2 would be expected. In addition, the Applicant provided a population pharmacokinetics analysis to compare the pharmacokinetic characteristics between the three tablet formulations (1, 2A, and 2). In general, the three tablet formulations showed similar systemic exposure based on population pharmacokinetic prediction (Figure 10). The population pharmacokinetics analysis was considered as a supportive evidence.

Figure 10. Formulation Effect on Bempedoic Acid AUC at Steady State, Trials 1002-046, 1002-047, and 1002-048 Combined PK



Source: Figure 11 in module 5.3.5.3 Data to Support Formulation Changes
The numbers in the box are median: AUC_{ss} units are hr*µg/mL. Boxes are the interquartile range and whiskers are 90th percentile range of observations. Circles are outliers.
Abbreviations: Form, formulation; n, number of subjects in group; PK, pharmacokinetics

Following oral administration, rapid release of bempedoic acid from the immediate-release formulations will result in insoluble bempedoic acid in the stomach. The solubility increases as bempedoic acid transits to a higher pH in the small intestine. In theory, food intake would increase retention time in the stomach, leading to prolonged dissolution and improved absorption. In addition, the intestinal solubility and absorption of bempedoic acid may decrease in the presence of bile salts that are secreted following the food intake. These effects are unlikely to be formulation dependent, as both the tablet formulation 1 and tablet formulation 2 (TBM formulation) have rapid and comparable in vitro dissolution profiles. Therefore, the differences in formulations are not expected to result in different food effect on drug absorption.

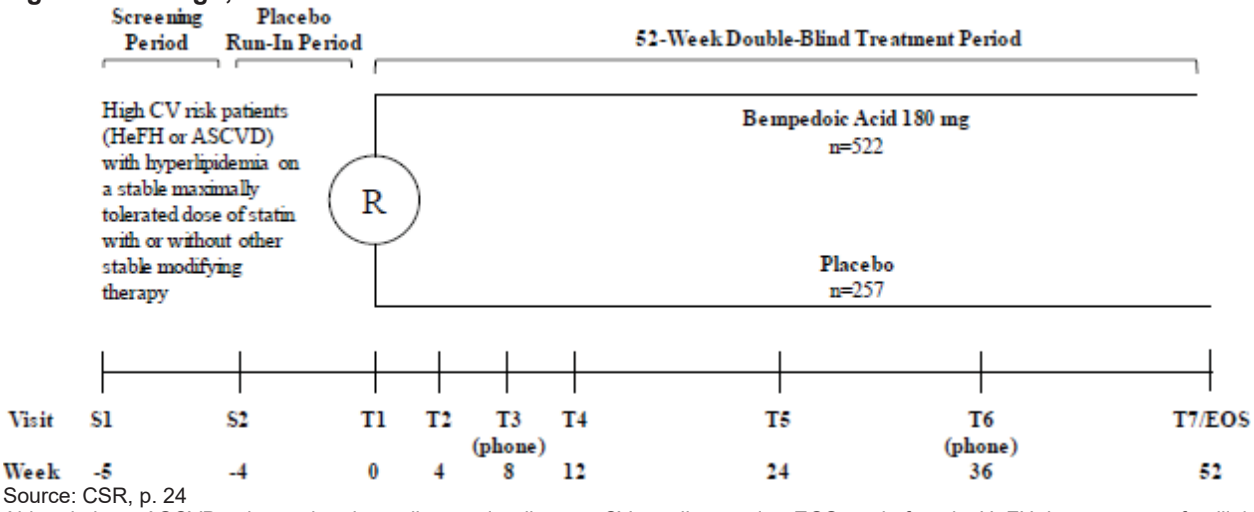
6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.2.1. Trial Design

The submission comprises four randomized, double-blind phase 3 studies. As previously described (Section 3.1), two trials were considered pivotal (Trials 040 and 047) and two trials were considered supportive (Trials 046 and 048). In all studies, subjects were randomized in a 2:1 ratio to receive bempedoic acid 180 mg or placebo. The primary efficacy endpoint in all trials was reduction in LDL-C from baseline to Week 12.

Trials 040 and 047 were designed as 52-week, randomized, double-blind, placebo-controlled, multicenter trials to evaluate bempedoic acid versus placebo in patients with hyperlipidemia at high cardiovascular risk whose LDL-C was not adequately controlled by baseline lipid-modifying therapy. Randomization was stratified by HeFH status and baseline statin intensity. After randomization, patients were followed every 4 weeks for 3 months, then every 12 weeks. Trial 047 utilized a 4-week placebo run-in period for statin optimization and compliance assessment prior to randomization. Otherwise, the trial designs were similar. A general schematic description of Trial 047 is presented in Figure 11.

Figure 11. Design, Trial 1002-047



Source: CSR, p. 24
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; EOS, end of study; HeFH, heterozygous familial hypercholesterolemia; n, number of subjects in group; s, screening visit; t, treatment visit

Two short-term trials, Trials 046 (24 weeks) and 048 (12 weeks), were conducted in "statin-intolerant" patients with primary hyperlipidemia who required LDL-C reduction for primary or secondary prevention. In Trial 046, randomization was stratified by primary versus secondary prevention. Both trials included a 4-week placebo run-in period for compliance. In Trial 048, enrolled patients were started on background ezetimibe pre-randomization to evaluate bempedoic acid's effect in combination with ezetimibe. Otherwise, the trial designs were similar.

General schematic descriptions of all four studies are presented in Section 15.

Primary Endpoint

In each study, percent change in LDL-C from baseline to Week 12 was the primary efficacy endpoint. LDL-C reduction is a surrogate endpoint for CV risk reduction and has been used as the basis for approval in previous trials of lipid-lowering drugs.

LDL-C was calculated using the Friedewald equation, which is generally considered reliable within <0.5 mg/dL of directly-measured LDL. For patients with TG >400 mg/dL or LDL-C ≤50 mg/dL, the Friedewald equation loses accuracy; in these cases, direct LDL measurement was used. No adjustment to background lipid-modifying therapy (LMT) was allowed during the trials until after assessment of the primary endpoint.

Key Secondary and Exploratory Endpoints

All phase 3 studies evaluated the percent change in non-HDL-C, TC, Apo-B, and hsCRP from baseline to Week 12 as secondary endpoints.

In clinical practice, TC and Apo-B may be considered in treatment decisions regarding CV risk optimization. However, the utility of non-HDL-C as a biomarker is less clear. Review of changes to non-HDL-C's components, LDL-C and very LDL (TG carrier), are more clinically meaningful. Note also that the Division does not currently consider reduction in hsCRP as a surrogate endpoint for any clinically meaningful outcome.

Other endpoints of interest to practicing clinicians are changes in TG and HDL from baseline. The Applicant did not include these biomarkers as prespecified secondary endpoints, however, the review team evaluated them as exploratory endpoints.

6.2.2. Eligibility Criteria

Trials 040 and 047 were trials in subjects with high CV risk whose LDL-C was ≥70 mg/dL at randomization despite use of maximally tolerated statins and who required additional lowering for secondary prevention. Key inclusion and exclusion criteria are listed below.

Key Inclusion Criteria, High CV Risk Trials

1. Age ≥18 years
2. High cardiovascular risk, defined as:
    a. HeFH (by genotyping, WHO criteria, or Simon Broome Register criteria [see Section 15])
    b. Atherosclerotic cardiovascular disease (ASCVD) (established or risk-equivalent CHD)
        i. Established CHD: history of acute or silent myocardial infarction (MI), unstable angina, coronary revascularization, or positive diagnostic testing
        ii. Risk-equivalent CHD: peripheral arterial disease, cerebrovascular disease
3. On maximally-tolerated, stable (>4 weeks) statin dose
4. Fasting LDL ≥70 mg/dL at randomization

Key Exclusion Criteria, High CV Risk Studies

1. Triglycerides ≥500 mg/dL
2. Recent (within 3 months) cardiovascular event or intervention
3. Uncontrolled hypertension
4. Active liver disease
5. Hemoglobin <10.0 g/dL at screening
6. Active malignancy within past 5 years
7. Renal dysfunction or eGFR <30 mL/min/1.73 m^2
8. HbA1c ≥10% at screening
9. Uncontrolled hypothyroidism
10. CK >3x upper limit of normal (ULN) at randomization
11. BMI ≥50 kg/m^2
12. Noncompliance (<80% of planned doses) with placebo run-in (Trial 047 only)
13. Use of the following concomitant medications
    a. Simvastatin doses ≥40 mg daily
    b. PCSK9 inhibitor within 4 weeks of screening; adjuvant use allowed after Week 24 (excluded from Trial 040 only, use allowed in Trial 047)
    c. CETP inhibitors within previous 2 years (excluded from Trial 047 only)
    d. Mipomersen, lomitapide, or apheresis
    e. Systemic corticosteroids, new or planned dose change
    f. Hormone replacement, new or planned dose change
    g. Thyroid replacement, new or planned dose change
    h. Diabetes medications, new or planned dose change
    i. Obesity medications, new or planned dose change

Trials 046 and 048 included patients with primary hyperlipidemia and "statin intolerance" who required LDL-C reduction for primary or secondary prevention. Note that the Division does not agree with the Applicant's definition of statin intolerance in these trials, which was identified by patient report rather than an a priori algorithm and did not include statin rechallenge. Furthermore, the Division does not agree with the Applicant's decision to restrict allowable statin doses to either the lowest approved dose (Trial 048) or less than the lowest approved dose (Trial 046), as this approach is inconsistent with current medical practice guidelines. As such, the clinical relevance of these short-term trial results is unclear.

Key Inclusion Criteria, No/Low Statin Trials

1. Age ≥18 years
2. Statin doses do not exceed
    a. Trial 046: very-low-dose statin, defined as an average daily dose less than the lowest approved statin doses (Section 15)

   b. Trial 048: low-dose statin
3. Fasting LDL at screening
   a. Trial 046
      i. Primary prevention, ≥130 mg/dL
      ii. Secondary prevention or HeFH, ≥100 mg/dL
   b. Trial 048
      i. On baseline ezetimibe, ≥100 mg/dL
      ii. No baseline ezetimibe, ≥120 mg/dL
4. Fasting LDL-C ≥70 mg/dL at randomization
5. Patient-reported statin intolerance
   a. Trial 046: inability to tolerate two or more statins, one at a low dose, due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin was discontinued
   b. Trial 048: attempting statin therapy and unable to tolerate it due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin was discontinued or the dose lowered

Key Exclusion Criteria, No/Low Statin Trials

1. Triglycerides ≥500 mg/dL
2. Recent (within 3 months) cardiovascular event or intervention
3. Uncontrolled hypertension
4. Active liver disease
5. Hemoglobin <10.0 g/dL at screening
6. Active malignancy within past 5 years
7. Renal dysfunction or eGFR <30 mL/min/1.73 m^2
8. HbA1c ≥10% at screening
9. Uncontrolled hypothyroidism
10. CK >3x ULN at randomization
11. BMI ≥50 kg/m^2
12. Noncompliance (<80% of planned doses) with placebo run-in
13. Use of the following concomitant medications
    a. Rosuvastatin ≥5 mg daily (Trial 046) or >5 mg daily (Trial 048)
    b. Atorvastatin ≥10 mg daily (Trial 046) or >10 mg daily (Trial 048)
    c. Simvastatin ≥10 mg daily (Trial 046) or >10 mg daily (Trial 048)
    d. Lovastatin ≥20 mg daily (Trial 046) or >2 0mg daily (Trial 048)
    e. Pravastatin ≥40 mg daily (Trial 046) or >40 mg daily (Trial 048)

f. Fluvastatin ≥40 mg daily (Trial 046) or >40 mg daily (Trial 048)
g. Pitavastatin ≥2 mg daily (Trial 046) or >2 mg daily (Trial 048)
h. PCSK9 inhibitor within 4 months of screening (excluded from Trial 048 only)
i. CETP inhibitors within previous 2 years
j. Mipomersen, lomitapide, or apheresis
k. Red yeast rice-containing products
l. Systemic corticosteroids, new or planned dose change
m. Hormone replacement, new or planned dose change
n. Thyroid replacement, new or planned dose change
o. Diabetes medications, new or planned dose change
p. Obesity medications, new or planned dose change

6.2.3. Statistical Analysis Plan

All efficacy analyses were conducted using all randomized subjects following the ITT principle. Subjects were included in their randomized treatment group, regardless of the treatment they received.

Control of Type-I Error

The study-wise type-I error was controlled at 5% using a step-down testing strategy. All endpoints were tested sequentially at alpha level of 0.05. Each endpoint was tested only if the previous endpoint was statistically significant. A detailed testing hierarchy is presented below.

Testing Hierarchy

Percent change from baseline in:

1. LDL-C (primary endpoint, Week 12)
2. LDL-C (Week 24)
3. At Week 12:
   a. non-HDL-C
   b. TC
   c. Apo-B
   d. hs-CRP

In addition to the prespecified secondary endpoints, the review team also examined changes in TG and HDL given the clinical relevance of these biomarkers.

Analyses of Primary Endpoint

The Applicant analyzed the percent change in LDL-C using an analysis of covariance (ANCOVA) model with treatment, randomization strata, and baseline value as covariates. Missing data were imputed using a pattern mixture model, where subjects who discontinued

treatment were considered to have similar post-discontinuation LDL-C levels as subjects on placebo, i.e., assuming that the data for subjects on treatment was missing at random.

The review team does not agree with the assumption that subjects who discontinued treatment early will have similar post-discontinuation biomarker levels as placebo. Therefore, for subjects in the treatment group, we conducted washout imputations without missing at random assumption. In this approach, the imputations were based on values obtained from the randomized treatment group. A step-by-step approach to washout imputations is presented below.

Imputation approach (retrieved dropouts, washout, ANCOVA)

1. First, 200 copies of the dataset were generated.
2. Imputations were stratified by treatment group, baseline statin, and cardiovascular status.
3. For subjects who had a missing LDL-C value at the primary endpoint and were treated with bempedoic acid, the 12-week endpoint imputation approach did not utilize the intermediate values (washout effect). For subjects on placebo, all values were included in the imputation procedure.
4. For each dataset separately, the change in LDL-C at Week 12 was analyzed using an ANCOVA model. Each ANCOVA model contained baseline statin and cardiovascular status and treatment group as covariates.
5. Results from an ANCOVA model fit to the imputed datasets were analyzed and combined using Rubin's method. Treatment effect estimates and limits from the 95% confidence interval (CI) were retained.

Sensitivity Analyses

Since Trial 040 had a sufficient number of retrieved dropouts, i.e., subjects who discontinued treatment early but continued study participation, we conducted sensitivity analyses using imputation based on biomarker level obtained from retrieved dropouts in each treatment group. For all other sensitivity analyses, we examined the data without imputations.

Secondary Endpoints

All secondary endpoints were analyzed using an ANCOVA model with treatment, randomization strata, and baseline value as covariate. Since hsCRP is not normally distributed, the Applicant utilized nonparametric testing procedures such as Wilcoxon Rank-sum test with Hodges-Lehman estimates. For the same reason, in our analyses, we also used this nonparametric approach in evaluation of changes in Triglycerides.

Subgroup Analyses

The review team conducted the subgroup analyses where the sample estimates of treatment effect in change of LDL-C among subgroups: age, sex, race and region, were obtained by using the same ANCOVA model as for the primary analysis. Similar analyses were conducted based on trial randomization strata (cardiovascular status in Trials 040 and 047 and prevention and/or HeFH status in Trial 046. The detailed numeric information on subgroup outcomes is presented in the Appendix (Section 16.3).

Additionally, shrinkage estimates of subgroup treatment effects were derived using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. The analysis utilized the same flat prior to derive shrinkage estimates for all subgroups.

Bayesian hierarchical model assumptions are:

For i=1, 2, …, Yi represents the observed sample estimate of treatment effect in subgroup level i, assuming $Yi \sim N(\mu i, \sigma i^2)$ where:

- σi^2 are observed variance for sample estimates
- $\mu i \sim N(\mu, \tau^2)$
- $\mu \sim N_{truncated}$(mean =0, std =100, lower limit of -100), $1/\tau^2 \sim$ Gamma(0.001, 0.001)

The standard deviation for μ was selected based on individual residual standard deviation multiplied by 4.

The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups are presented in the Appendix (Section 16.3). The subgroup treatment effects are consistent across subgroups and with the overall treatment effect. The estimates of treatment effects and their 95% confidence intervals were below zero for all of the subgroups.

6.3. Results of Analyses of Clinical Trials / Studies Intended to Demonstrate Benefit to Patients

This section summarizes patient disposition, demographics, baseline disease characteristics, and primary efficacy results based on data submitted by the Applicant.

All trials submitted as a part of the clinical program had a large percentage of screen failures, ranging from 34.3% in Trial 040 to 66.1% in Trial 047 (Table 8). The primary reason for screen failure was failure to meet LDL-C entry criteria, i.e., having a well-controlled LDL-C value that did not require additional lowering. Of note, most of the screen failures were identified at the first screening; only 5.8% of subjects in Trial 047 failed during run-in period. The high incidence of screen failures could signal potential issues of external validity and generalizability.

Table 8. Patient Screening and Randomization

Disposition	Trial 040	Trial 047	Trial 046	Trial 048
No. of patients screened	3395	2300	602	616
No. of patients not randomized	1165	1521	257	347
No. of screening failures	1165/3395 (34.3%)	1521/2300 (66.1%)	257/602 (42.7%)	347/616 (56.3%)
No. of patients randomized	2230	779	345	269

Source: ADSL.xpt, Tool: SAS

Of note, LDL-C ≥70 mg/dL at screening was required to participate in Trial 040. However, 2.6% (n=58) of subjects in that study had a baseline LDL-C below the required threshold. Given the small incidence, this is unlikely to impact efficacy interpretation.

Pivotal Trials: High CV Risk Pool (Trials 040 and 047)

No evidence of differential attrition was present in Trial 040, however, a greater proportion of bempedoic acid–treated patients withdrew from Trial 047 (Table 9). In both trials, more bempedoic acid–treated patients discontinued drug, most frequently due to adverse events.

Table 9. Patient Disposition, Pivotal Trials in High CV Risk Patients, Trial 040 and 047

	Trial 040		Trial 047	
Disposition Category	Bempedoic Acid N=1488 n (%)	Placebo N=742 n (%)	Bempedoic Acid N=522 n (%)	Placebo N=257 n (%)
Patients randomized	1488 (100.0)	742 (100.0)	522 (100.0)	257 (100.0)
ITT population	1488 (100.0)	742 (100.0)	522 (100.0)	257 (100.0)
Safety population	1487 (99.9)	742 (100.0)	522 (100.0)	257 (100.0)
Completed study[1]	1404 (94.4)	706 (95.2)	490 (93.9)	250 (97.3)
Discontinued study	84 (5.7)	36 (4.9)	32 (6.1)	7 (2.7)
Death	17 (1.1)	5 (0.7)	8 (1.5)	3 (1.2)
Adverse event	20 (1.3)	7 (0.9)	2 (0.4)	2 (0.8)
Withdrawal by patient	40 (2.7)	23 (3.1)	6 (1.2)	1 (0.4)
Protocol deviation	2 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)
Lost to follow-up	2 (0.1)	1 (0.1)	9 (1.7)	1 (0.4)
Physician decision	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Applicant decision	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)
Completed drug	1142 (76.8)	600 (80.9)	415 (79.5)	214 (83.3)
Discontinued drug	346 (23.2)	142 (19.1)	107 (20.5)	43 (16.7)
Death	6 (0.4)	2 (0.3)	3 (0.6)	1 (0.4)
Adverse event	155 (10.8)	55 (7.4)	54 (10.3)	21 (8.2)
Withdrawal by patient	95 (6.5)	51 (6.9)	27 (5.2)	11 (4.3)
Applicant decision	71 (4.8)	32 (4.3)	3 (0.6)	1 (0.4)
Physician decision	12 (0.8)	0 (0.0)	5 (1.0)	6 (2.3)
Protocol deviation	3 (0.2)	2 (0.3)	5 (1.0)	1 (0.4)
Lost to follow-up	2 (0.1)	1 (0.1)	7 (1.3)	1 (0.4)
Other	2 (0.1)	1 (0.1)	3 (0.6)	1 (0.4)
Completed study[2] based on the primary endpoint (LDL-C)	1364 (91.7)	685 (92.3)	467 (89.5)	237 (92.2)

Source: adsl.xpt; Software: JMP
[1] Subjects who did not withdraw consent during the study. These table entries do not account for availability of safety and efficacy data at the end of the trial.
[2] Week 52
Abbreviations: ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group; n, number of subjects in given category with at least one event.

Baseline demographics and disease characteristics were well-balanced between treatment arms in the pivotal trials. Of note, both studies had a disproportionally low number of female subjects (approximately 30%). Most patients were non-Hispanic and white with a mean age of 65 years. One-third of study participants were from North America, and 26% were from the United States. Most trial patients were overweight, were either former or current smokers, had hypertension, and had at least mild renal impairment based on eGFR. Approximately one-third of patients had diabetes.

Most patients enrolled in the trials had established ASCVD (94% to 95%), while a small percentage (approximately 5%) had HeFH. Mean baseline LDL-C values were 103.2 mg/dL in Trial 040 and 120.4 mg/dL in Trial 047. Most patients (90% to 100%) were on statin therapy at baseline, and 50% to 53% of patients were on high-intensity statin. Table 10 and Table 11 show the demographic and baseline disease characteristics of enrolled subjects in the pivotal trials.

Table 10. Baseline Demographics and Clinical Characteristics, ITT Population, Trials 040 and 047

	Trial 040		Trial 047	
Demographic Characteristic	**Bempedoic Acid (N=1488)**	**Placebo (N=742)**	**Bempedoic Acid (N=522)**	**Placebo (N=257)**
Age, years				
Mean (SD)	65.8 (9.1)	66.8 (8.6)	64.1 (8.8)	64.7 (8.7)
Median (min, max)	67.0 (24, 88)	67.0 (38, 88)	64.0 (37, 91)	65.0 (28, 86)
Sex, n (%)				
Female	389 (26.1)	213 (28.7)	194 (37.2)	89 (34.6)
Male	1099 (73.9)	529 (71.3)	328 (62.8)	168 (65.4)
Race, n (%)				
American Indian or Alaska native	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.4)
Asian	14 (0.9)	8 (1.1)	4 (0.8)	0 (0.0)
Black	42 (2.8)	15 (2.0)	24 (4.6)	12 (4.7)
Multiple	1 (0.1)	0 (0.0)	2 (0.4)	0 (0.0)
Native Hawaiian or Pacific Islander	2 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Other	4 (0.3)	2 (0.3)		
White	1423 (95.6)	716 (96.5)	491 (94.1)	244 (94.9)
Ethnicity, n (%)				
Hispanic	24 (1.6)	11 (1.5)	43 (8.2)	19 (7.4)
Not Hispanic	1464 (98.4)	731 (98.5)	479 (91.8)	238 (92.6)
Region, n (%)				
Europe	981 (65.9)	483 (65.1)	367 (70.3)	185 (72.0)
North America	507 (34.1)	259 (34.9)	155 (29.7)	72 (28.0)
Country, n (%)				
United States	372 (25.0)	188 (25.3)	145 (27.8)	68 (26.5)
Other countries	1115 (75.0)	554 (74.7)	377 (72.2)	189 (73.5)
History of diabetes, n (%)				
No	1063 (71.4)	530 (71.4)	367 (70.3)	176 (68.5)
Yes	425 (28.6)	212 (28.6)	155 (29.7)	81 (31.5)
History of hypertension, n (%)				
No	314 (21.1)	148 (19.9)	84 (16.1)	33 (12.8)
Yes	1174 (78.9)	594 (80.1)	438 (83.9)	224 (87.2)
Tobacco history, n (%)				
Current	251 (16.9)	103 (13.9)	110 (21.1)	57 (22.2)
Former	742 (49.9)	405 (54.6)	214 (41.0)	109 (42.4)
Never user	484 (32.5)	230 (31.0)	198 (37.9)	91 (35.4)
Missing	11 (0.7)	4 (0.5)		
eGFR category at baseline, n (%)				
15-<30 mL/min/1.73m2			1 (0.2)	1 (0.4)
30-<60 mL/min/1.73m2	222 (14.9)	107 (14.4)	76 (14.6)	36 (14.0)
60-<90 mL/min/1.73m2	946 (63.6)	468 (63.1)	338 (64.8)	164 (63.8)
≥90 mL/min/1.73m2	320 (21.5)	167 (22.5)	107 (20.5)	56 (21.8)
BMI at baseline (kg/m^2)				
Mean (SD)	29.7 (4.9)	29.4 (4.9)	30.0 (5.2)	30.6 (5.0)
Median (min, max)	29.1 (18.5, 50.1)	28.9 (16.4, 53.7)	29.4 (18.7, 49)	29.9 (20, 47.8)

Source:ADSL.xpt, Tool: SAS
Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; N, number of subjects in group; n, number of subjects with given characteristic; SD, standard deviation

Table 11. Baseline Disease Characteristics, ITT Population, Trials 040 and 047

	Trial 040		Trial 047	
Disease Characteristic	**Bempedoic Acid (N=1488)**	**Placebo (N=742)**	**Bempedoic Acid (N=522)**	**Placebo (N=257)**
Cardiovascular history/risk factor, n (%)				
ASCVD	1415 (95.1)	707 (95.3)	495 (94.8)	241 (93.8)
HeFH	73 (4.9)	35 (4.7)	27 (5.2)	16 (6.2)
Baseline lipid-modifying therapy (LMT), n (%)				
Statin alone	1270 (85.4)	641 (85.4)	416 (79.7)	196 (83.9)
Statin + other LMT	214 (14.4)	101 (13.6)	54 (10.3)	32 (12.5)
Other LMT alone	2 (0.1)	0 (0.0)	22 (4.2)	15 (5.8)
None	1 (0.1)	0 (0.0)	30 (5.7)	14 (5.4)
Baseline statin intensity, n (%)				
High	742 (49.9)	370 (49.9)	278 (53.3)	135 (52.5)
Moderate	646 (43.4)	324 (43.7)	166 (31.8)	82 (31.9)
Low	100 (6.7)	48 (6.5)	78 (14.9)	40 (15.6)
Baseline PCSK9 inhibitor, n (%)				
No	1488 (100.0)	742 (100.0)	520 (99.6)	255 (99.2)
Yes	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.8)
Baseline ezetimibe use, n (%)				
No	1357 (91.2)	677 (91.2)	484 (92.7)	233 (90)
Yes	131 (8.8)	65 (8.8)	38 (7.3)	24 (9.3)
LDL-C (mg/dL) at baseline				
Mean (SD)	104 (29.1)	102 (30.0)	119 (37.7)	122 (38.3)
Median (min, max)	96.0 (52, 357)	95.0 (55, 411)	113 (41.5, 407)	113 (58.5, 327)
Triglycerides (mg/dL) at baseline				
Mean (SD)	142 (67.4)	140 (64.1)	162 (89.5)	161 (79.4)
Median (min, max)	127 (44, 874)	123 (51, 560)	139 (45, 744)	143 (35, 581)
HDL-C (mg/dL) at baseline				
Mean (SD)	48.7 (11.8)	49.3 (11.5)	51.4 (12.9)	51.1 (13.1)
Median (min, max)	47.0 (18, 106)	47.5 (22, 105)	49.8 (21, 116)	49.5 (25, 104)
Total cholesterol (mg/dL) at baseline				
Mean (SD)	180 (35.2)	179 (35.6)	202 (42.7)	205 (46.1)
Median (min, max)	172 (120, 452)	172 (120, 501)	195 (102, 497)	198 (121, 409)
Non-HDL-cholesterol (mg/dL) at baseline				
Mean (SD)	131 (33.7)	129 (33.9)	151 (42.7)	154 (44.4)
Median (min, max)	124 (70.5, 396)	123 (81.5, 431)	142 (45.5, 436)	146 (87, 345)
Apolipoprotein B (mg/dL) at baseline				
Mean (SD)	88.5 (21.6)	86.8 (21.8)	116 (29.6)	119 (30.5)
Median (min, max)	84.0 (25, 235)	83.0 (49, 243)	111 (45, 296)	113 (54, 240)
hsCRP (mg/L) at baseline				
Mean (SD)	3.5 (8.2)	3.3 (7.2)	3.0 (4.3)	3.7 (5.6)
Median (min, max)	1.5 (0.1, 185)	1.5 (0.1, 121)	1.6 (0.1, 44.8)	1.9 (0.1, 48.4)

Source:ADSL.xpt, Tool: SAS
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group; n, number of subjects with given characteristic; SD, standard deviation

Supportive Trials: No/Low Statin Pool (1002-046 and 1002-048)

No evidence of differential attrition was present in Trial 048; however, more bempedoic acid–treated patients withdrew from Trial 046 due to adverse events (Table 12). In both trials, more bempedoic acid patients discontinued drug, and the majority of these patient discontinued due to adverse events. Of note, the discontinuation incidence due to adverse events was higher in the no/low statin pool than in the high CV risk pool. This may be due to inherent differences in the no/low statin pool trial population, which includes patients with self-reported statin intolerance.

Table 12. Patient Disposition, Supportive Trials in Primary Hyperlipidemia, Trial 046 and 048

	Trial 046		Trial 048	
Disposition Category	Bempedoic Acid N=234 n (%)	Placebo N=111 n (%)	Bempedoic Acid N=181 n (%)	Placebo N=88 n (%)
Patients randomized	234 (100.0)	111 (100.0)	181 (100.0)	88 (100.0)
ITT population	234 (100.0)	111 (100.0)	181 (100.0)	88 (100.0)
Safety population	234 (100.0)	111 (100.0)	181 (100.0)	88 (100.0)
Completed study[1]	220 (94.0)	107 (96.4)	176 (97.2)	81 (92.0)
Discontinued study	14 (6.0)	4 (3.6)	5 (2.8)	7 (8.0)
Adverse event	6 (2.6)	1 (0.9)	3 (1.7)	3 (3.4)
Withdrawal by patient	1 (0.4)	1 (0.9)	0 (0.0)	2 (2.3)
Applicant decision	5 (2.1)	2 (1.8)	0 (0.0)	1 (1.1)
Lost to follow-up	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)
Other	2 (0.9)	0 (0.0)	0 (0.0)	1 (1.1)
Completed drug	176 (75.2)	93 (83.8)	164 (90.6)	79 (89.8)
Discontinued drug	58 (24.8)	18 (16.2)	17 (9.4)	8 (9.1)
Adverse event	43 (18.4)	13 (11.7)	13 (7.2)	5 (5.7)
Withdrawal by patient	3 (1.3)	3 (2.7)	1 (0.6)	2 (2.3)
Applicant decision	5 (2.1)	2 (1.8)	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)
Other	7 (3.0)	0 (0.0)	0 (0.0)	1 (1.1)
Never received drug	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Completed study[2] based on the primary endpoint (LDL-C)	217 (92.7)	106 (95.5)	175 (96.7)	82 (93.2)

Source: adsl.xpt; Software: JMP
[1] Subjects who did not withdraw consent during the study. These table entries do not account for availability of safety and efficacy data at the end of the trial.
[2] Week 24 for Trial 046 and Week 12 for Trial 048
Abbreviations: ITT, modified intention-to-treat; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group; n, number of subjects in given category with at least one event

Demographics and baseline disease characteristics were also well-balanced between treatment arms in the short-term trials. Fifty percent (50%) of patients were women, and most patients were non-Hispanic and white. The majority (70% or more) of patients were from North America. Most trial patients were overweight, did not have a diagnosis of diabetes, had hypertension, and had mild renal impairment based on eGFR. Less than half of subjects were current or former smokers (32% to 44%).

Most patients were enrolled in the trials for primary prevention, while only 25% to 40% were enrolled for secondary prevention. Mean baseline LDL-C values were 157.6 mg/dL in Trial 046

and 127.6 mg/dL in Trial 048. More than half of patients were on no lipid-modifying therapy at baseline (50% to 58%). In Trial 046, only 8% of patients were on very-low-dose statin at enrollment, while in Trial 048, 31% of patients were on very-low-dose or low-dose statins.

Given the large percentage of patients on no antihyperlipidemia therapy at baseline, the Division does not consider the enrolled patient population in these trials to be reflective of the intended primary hyperlipidemia population. In clinical practice, standard of care therapy for hyperlipidemia is initiation of statin therapy (depending on baseline risk for CVD) with addition of ezetimibe or PCSK9 inhibitors as add-on therapy for patients who require additional LDL-C lowering. As such, we would expect most patients to be on baseline LMT.

Table 13 and Table 14 show the demographics and baseline disease characteristics of enrolled subjects in the supportive trials.

Table 13. Baseline Demographic and Clinical Characteristics, ITT Population, Trials 046 and 048

	Trial 046		Trial 048	
Baseline Characteristic	**Bempedoic Acid (N=234)**	**Placebo (N=111)**	**Bempedoic Acid (N=181)**	**Placebo (N=88)**
Age, years				
Mean (SD)	65.2 (9.7)	65.1 (9.2)	63.8 (10.8)	64.0 (11.2)
Median (min, max)	66.0 (26, 88)	66.0 (39, 86)	66.0 (30, 85)	66.0 (32, 86)
Sex, n (%)				
Female	133 (56.8)	61 (55.0)	109 (60.2)	56 (63.6)
Male	101 (43.2)	50 (45.0)	72 (39.8)	32 (36.4)
Race, n (%)				
American Indian or Alaska native	1 (0.4)	0 (0.0)		
Asian	6 (2.6)	2 (1.8)	3 (1.7)	1 (1.1)
Black	16 (6.8)	10 (9.0)	11 (6.1)	10 (11.5)
Multiple	0 (0.0)	1 (0.9)	0 (0.0)	2 (2.3)
Native Hawaiian or Pacific Islander	0 (0.0)	2 (1.8)	2 (1.1)	0 (0.0)
Other				
White	211 (90.2)	96 (86.5)	165 (91.2)	75 (85.1)
Ethnicity, n (%)				
Hispanic	13 (5.6)	4 (3.6)	43 (23.8)	23 (26.1)
Not Hispanic	221 (94.4)	107 (96.4)	138 (76.2)	65 (73.9)
Region, n (%)				
Europe			34 (18.8)	15 (17.0%)
North America	234 (100)	111 (100)	136 (75.1)	67 (76.1%)
Country, n (%)				
United States	173 (73.9)	78 (70.3)	136 (75.1)	66 (75.9)
Other countries	61 (26.1)	33 (29.7)	45 (24.8)	21 (24.1)
History of diabetes, n (%)				
No	171 (73.1)	85 (76.6)	146 (80.7)	71 (80.7)
Yes	63 (26.9)	26 (23.4)	35 (19.3)	17 (19.3)
History of hypertension, n (%)				
No	76 (32.5)	36 (32.4)	70 (38.7)	37 (42.0)
Yes	158 (67.5)	75 (67.6)	111 (61.3)	51 (58.0)

Baseline Characteristic	Trial 046		Trial 048	
	Bempedoic Acid (N=234)	Placebo (N=111)	Bempedoic Acid (N=181)	Placebo (N=88)
Tobacco history, n (%)				
Current	30 (12.8)	11 (9.9)	21 (11.6)	12 (13.6)
Former	73 (31.2)	35 (31.5)	48 (26.5)	22 (25.0)
Never	131 (56.0)	65 (58.6)	112 (61.9)	54 (61.4)
eGFR category at baseline, n (%)				
15-<30 mL/min/1.73m2	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)
30-<60 mL/min/1.73m2	36 (15.4)	26 (23.4)	25 (13.8)	14 (15.9%)
60-<90 mL/min/1.73m2	139 (59.4)	69 (62.2)	110 (60.8)	57 (64.8%)
≥90 mL/min/1.73m2	58 (24.8)	16 (14.4)	45 (24.9)	17 (19.3%)
BMI at Baseline (Kg/m^2)				
Mean (SD)	30.1 (5.8)	30.6 (5.2)	29.5 (4.7)	30.5 (5.8)
Median (min, max)	29.7 (17, 47.6)	29.7 (22.3, 49.9)	29.1 (17.8, 46.9)	29.1 (21.5, 50.1)

Source: ADSL.xpt, Tool: SAS
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; N, number of subjects in group; n, number of subjects with given characteristic; SD, standard deviation

Table 14. Baseline Disease Characteristics, ITT Population, Trials 046 and 048

Disease Characteristic	Trial 046		Trial 048	
	Bempedoic Acid (N=234)	Placebo (N=111)	Bempedoic Acid (N=181)	Placebo (N=88)
ASCVD category[1], n (%)				
Primary prevention	144 (61.5)	67 (60.4)	138 (76.2)	69 (78.4)
Secondary prevention	90 (38.5)	44 (39.6)	43 (23.8)	19 (21.6)
Baseline LMT, n (%)				
Statin alone	16 (6.8)	10 (9.0)	57 (31.5)	20 (23.0)
Statin + other LMT	2 (0.9)	1 (0.9)	2 (1.1)	4 (4.6)
Other LMT alone	83 (35.5)	33 (29.7)	27 (14.9)	10 (11.5)
None	133 (56.8)	67 (60.4)	95 (52.5)	54 (61.4)
Baseline statin intensity[2], n (%)				
High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	8 (3.4)	5 (4.5)	32 (17.7)	16 (18.2)
Low	4 (1.7)	4 (3.6)	22 (12.2)	8 (9.1)
Less than low[3]	6 (2.6)	2 (1.8)	4 (2.2)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Baseline ezetimibe use, n (%)				
No	200 (85.5)	96 (86.5)	89 (49.2)	56 (63.6)
Yes	34 (14.5)	15 (13.5)	92 (50.8)	32 (36.4)
Baseline PCSK9 inhibitor, n (%)				
No	230 (98.3)	110 (99.1)	NA	
Yes	4 (1.7)	1 (0.9)		
LDL-C (mg/dL) at baseline				
Mean (SD)	158 (40.4)	156 (38.8)	130 (30.9)	123 (27.3)
Median (min, max)	155 (75, 340)	153 (83, 311)	127 (54, 269)	119 (66.5, 205)
Triglycerides (mg/dL) at baseline				
Mean (SD)	179 (87.5)	187 (96.2)	167 (75.7)	144 (61.7)
Median (min, max)	157 (49, 603)	164 (74.5, 505)	153 (50, 460)	136 (55, 372)
HDL-Cl (mg/dL) at baseline				
Mean (SD)	52.2 (14.5)	50.4 (14.4)	55.8 (16.3)	57.0 (21.4)
Median (min, max)	49.3 (22, 106)	48.0 (24, 102)	54.0 (9.5, 113)	53.0 (34.5, 227)

Disease Characteristic	Trial 046 Bempedoic Acid (N=234)	Trial 046 Placebo (N=111)	Trial 048 Bempedoic Acid (N=181)	Trial 048 Placebo (N=88)
Total cholesterol (mg/dL) at baseline				
Mean (SD)	246 (47.3)	241 (44.3)	218 (35.9)	209 (35.7)
Median (min, max)	243 (154, 439)	239 (147, 395)	215 (126, 357)	204 (125, 356)
Non-HDL-C (mg/dL) at baseline				
Mean (SD)	193 (45.1)	191 (43.8)	162 (35.4)	152 (32.7)
Median (min, max)	191 (105, 367)	184 (105, 364)	159 (83, 320)	147 (80.5, 245)
Apolipoprotein B (mg/dL) at baseline				
Mean (SD)	141 (31.6)	142 (30.4)	123 (26.5)	116 (23.5)
Median (min, max)	139 (73, 274)	138 (81, 263)	122 (68, 232)	115 (60, 181)
hsCRP (mg/L) at baseline				
Mean (SD)	5.6 (15.9)	4.2 (5.1)	3.7 (4.9)	3.4 (3.3)
Median (min, max)	2.9 (0.2, 213)	2.8 (0.2, 35.3)	2.2 (0.2, 39.2)	2.3 (0.1, 14.4)

Source: ADSL.xpt, ADCM.xpt, ADMH.xpt Tool: SAS, JMP
[1] For Trial 048, designated by review of PMH for diagnoses of ASCVD, PAD, or CVA.
[2] Note that FDA used 2018 AHA/ACC classifications for high/moderate/low intensity, which varied slightly from the Applicant's definition (Appendix).
[3] Indicates doses that are less than the lowest FDA-approved dose.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; N, number of subjects in treatment group; n, number of subjects with given characteristic; NA, not applicable; SD, standard deviation

Missing Data

The missing data patterns in all four clinical studies are presented in Table 15. The Week 12 missing data were less than 5% in each of the treatment arms. The amount of missing data for subjects on placebo was smaller than the amount of missing data for subjects on treatment. The fraction of missing subjects at the end of both 52-week trials was two or more times larger than at the time of the Week 12 endpoint. The primary reason for missing data was premature discontinuation due to an adverse drug event

Table 15. Missing Data Patterns

Study/ Week	Bempedoic Acid Missing On	Bempedoic Acid Missing Off	Bempedoic Acid Total	Bempedoic Acid Died	Placebo Missing On	Placebo Missing Off	Placebo Total	Placebo Died
40 (n=2230)								
12	14	50	64 (4.3%)	4	5	12	17 (2.3%)	1
52	8	116	124 (8.3%)	17[1]	7	50	57 (7.7%)	5[1]
47 (n=779)								
12	9	15	24 (4.6%)	2	2	2	4 (1.6%)	1
52	7	48	55 (10.5%)	8[1]	2	18	20 (7.8%)	3[1]
46 (n=345)								
12	3	7	10 (4.3%)		1	3	4 (3.6%)	
24	3	14	17 (7.3%)		2	3	5 (4.5%)	
48 (n=269)								
12	0	6	6 (3.3%)		1	5	6 (6.8%)	

Source: adlbchem.xpt, ADSL.xpt, Tool: SAS
[1] Includes subjects who died after the trial
Abbreviations: n, number of subjects in study; On: on drug; Off: off drug

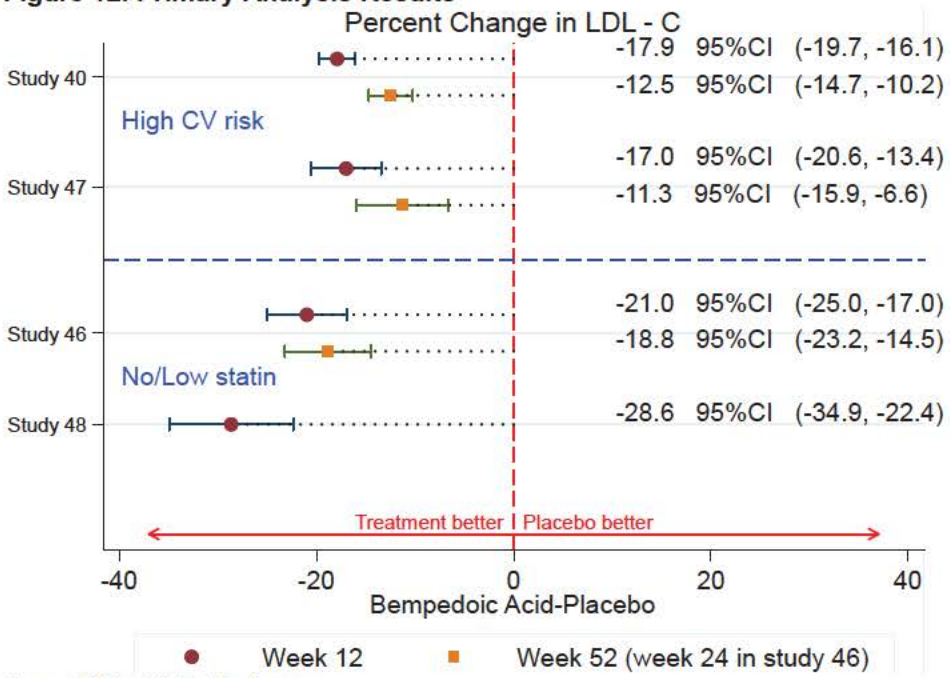
Primary Efficacy Results

The review team was able to replicate the Applicant's primary analyses and reanalyzed the data using washout imputations. Because of the relatively small amount of missing data observed at the 12-week primary endpoint, the results were similar no matter what imputation approach was implemented. All trials demonstrated that treatment with bempedoic acid was superior to placebo at Week 12. Of note, the effect was smaller in subjects on background statins (Trials 040 and 047).

Adjustment to background LMT was allowed beginning at Week 24. In both trials, more placebo-treated patients than bempedoic acid–treated patients experienced drop-in use of alternative LMT (9.6% placebo versus 8.4% bempedoic acid in Trial 040, 13.2% placebo versus 11.7% bempedoic acid in Trial 047). While the efficacy reduced after Week 12, treatment with bempedoic acid remained superior to placebo at Week 52.

The detailed description of efficacy outcomes by study and treatment group is presented in the Appendix (Section 16.1).

Figure 12. Primary Analysis Results



Source: FDA statistical reviewer
Legend: A forest plot of changes in LDL-C by study using the results from ANCOVA analyses that included washout imputations. The estimates of LDL-C changes at Week 12 are denoted by red circles and the estimates of LDL-C changes at the end of the trial, Week 52 (Week 24 for Trial 046) are denoted by yellow squares. The 95% confidence intervals are denoted by black lines. The red vertical line which corresponds to the value of zero is the line of no effect. The right panel of the graph provides the detailed numeric information.
Abbreviations: CI, confidence interval; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol

Analysis of Secondary and Exploratory Endpoints

This section summarizes results from the analyses of key secondary and exploratory endpoints. All results presented in this section are based on ANCOVA analysis without imputations. Because hsCRP did not have a normal distribution, the analyses for that biomarker were based on a nonparametric Hodges-Lehmann approach.

The changes in lipid biomarkers, expressed as placebo-adjusted percent change from baseline, are presented in Table 16 and Table 17 Of note, since there were no imputations performed for the analyses of all secondary endpoints, the changes in LDL-C presented in this section are similar but not identical to the results in the primary analyses. The change from baseline in each of the lipid markers in the original units, as well as data from Week 52, are presented in the Appendix (Section 16.2).

Table 16. Placebo-Adjusted Percent Change From Baseline for Key Secondary and Exploratory Endpoints, Week 12

Percent Change From Baseline	Trial 040	Trial 047	Trial 046	Trial 048
LDL-C[1]	-18.7 (-20.5, -16.9)	-17.9 (-21.5, -14.4)	-22.0 (-26.0, -17.9)	-29.4 (-35.7, -23.0)
HDL	-5.9 (-7.0, -4.7)	-6.1 (-8.5, -3.8)	-4.6 (-8.0, -1.2)	-5.9 (-9.8, -1.9)
Triglycerides	2.5 (-0.1, 5.1)	1.3 (-3.9, 6.3)	-0.1 (-7.0, 6.9)	-6.4 (-14.3, 1.4)
Apo-B[1]	-12.4 (-14.0, -10.8)	-13.5 (-16.4, -10.5)	-15.3 (-18.7, -11.9)	-19.9 (-24.8, -14.9)
Total cholesterol[1]	-11.5 (-12.8, -10.3)	-11.5 (-13.9, -9.2)	-15.1 (-17.9, -12.4)	-18.4 (-22.6, -14.2)
Non-HDL-C[1]	-13.8 (-15.5, -12.1)	-13.4 (-16.6, -10.2)	-18.4 (-21.8, -14.9)	-24.2 (-29.8, -18.6)
hsCRP[1]	-21.5[2](-26.9, -16)[3]	-8.7[2](-17.2, -0.4)[3]	-24.3[2](-35.9, -12.7)[3]	-31.0[2](-44.8, -17.4)[3]

Source: FDA reviewer analyses; Software SAS
[1] Prespecified endpoint;
[2] Location shift;
[3] Asymptotic 95%CI
Abbreviations: Apo-B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol

Table 17. Placebo-Adjusted Percent Change From Baseline for Key Secondary and Exploratory Endpoints, Week 24

Percent Change From Baseline	Trial 040	Trial 047	Trial 046
LDL-C[1]	-16.9 (-18.9, -14.9)	-15.7 (-20.6, -10.9)	-20.0 (-24.4, -15.7)
HDL	-5.4 (-6.7, -4.2)	-5.2 (-7.8, -2.7)	-5.6 (-9.5, -1.8)
Triglycerides	0.8 (-1.9, 3.5)	-1.9 (-7.0, 3.1)	-3.7 (-11.1, 3.9)
Apo-B[1]	-11.4 (-13.2, -9.7)	-13.1 (-17.7, -8.5)	-15.5 (-19.1, -12.0)
Total cholesterol[1]	-10.9 (-12.3, -9.5)	-10.8 (-13.7, -7.9)	-14.5 (-17.5, -11.5)
Non-HDL-C[1]	-13.1 (-14.9, -11.3)	-12.6 (-16.6, -8.6)	-17.1 (-20.8, -13.4)
hsCRP[1]	-19.5[2](-25.4, -13.7)[3]	-21.3[2](-32.2, -10.0)[3]	-27.1[2](-40.5, -13.7)[3]

Source: FDA reviewer analyses; Software SAS
[1] Prespecified endpoint;
[2] Location shift;
[3] Asymptotic 95%CI
Abbreviations: Apo-B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol

Overall, all secondary endpoints were achieved based on the prespecified testing hierarchy; changes in TC, non-HDL-C, and Apo-B were consistent with changes in LDL, but not additionally informative. The clinical significance of changes in hsCRP is unclear.

As in the primary analysis, subjects who were not on statin therapy at baseline (Trials 046 and 048) had a larger reduction in LDL-C, both at Weeks 12 and 24. The directionalities of Apo-B, hsCRP, and TC were similar among all four trials, i.e., all trials demonstrated a reduction, and the effect was larger amongst subjects who were not on baseline statin.

A reduction in HDL during the treatment was observed in all trials. Although statistically significant, the clinical significance of this reduction is unclear. More detailed information that includes treatment-specific change in the secondary endpoints (percent change and changes based on the original scale) is presented in the Appendix (Section 16.2).

Subgroup Analyses

The subgroup treatment effects were consistent across subgroups and with the overall treatment effect. Bempedoic acid's treatment effect was consistent regardless of baseline CV risk category, baseline LDL value, baseline lipid-modifying therapy, and baseline statin intensity. The detailed subgroup results are presented in the Appendix (Section 16.3).

6.4. Review Issues Relevant to Evaluation of Benefit

6.4.1. Demonstration of Efficacy

Issue

Sufficiency of data to demonstrate a clinically meaningful reduction in LDL-C with bempedoic acid treatment.

Conclusion

Bempedoic acid's treatment effect on LDL-C reduction is clinically meaningful.

Assessment

The above conclusion is based on the following assessments:

- Pivotal studies (Trials 040 and 047) achieved statistical significance in the primary endpoint
- Bempedoic acid lowered LDL-C in high CV risk patients on a background of maximally tolerated statins, most moderate- to high-intensity, who required additional LDL-C lowering
- LDL-C reduction is generally considered a surrogate for reduction in risk for CV events
- Although the treatment effect is modest (15% to 20% LDL-C reduction), bempedoic acid may represent an additional option in patients unable to meet goals with currently available therapy (statins, ezetimibe, or PCSK9i)

(b) (4)

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6.4.4. Changes to Other Biomarkers

Issue

No clinically meaningful impact on other endpoints of interest.

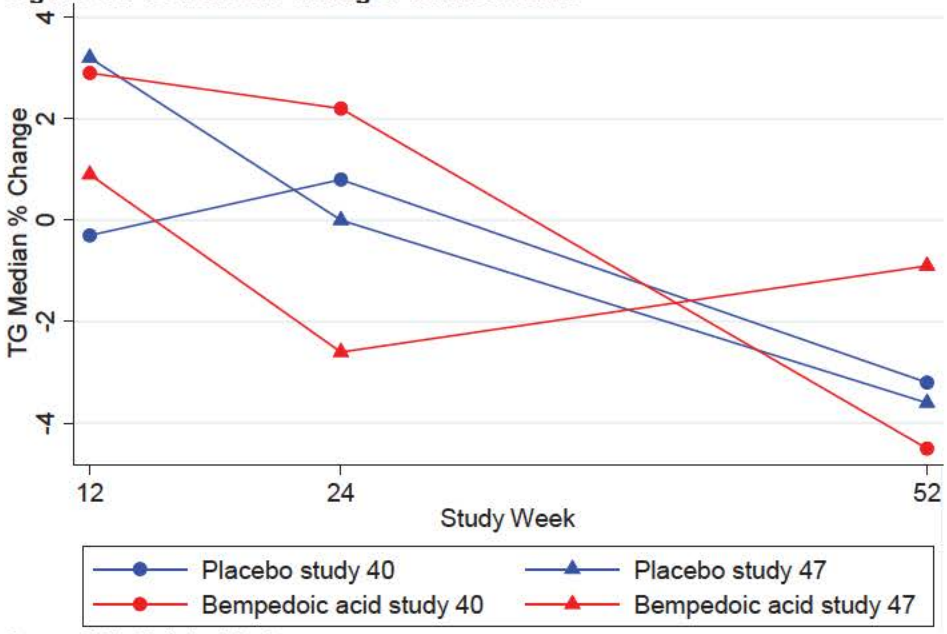
Conclusion

Bempedoic acid lowers LDL-C; effects on TC and Apo-B are consistent with changes in LDL-C, but do not infer any additional benefit; there were no meaningful changes in TG or HDL, and changes in these parameters are of uncertain significance. Changes in hsCRP are of unclear significance, as median hsCRP was not elevated at baseline.

Assessment

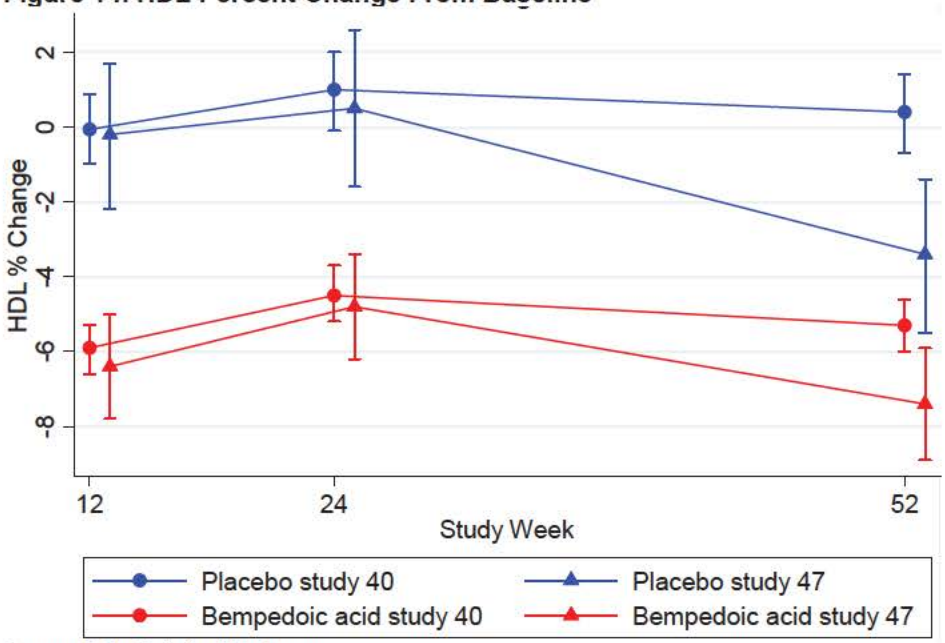
There were no clinically meaningful changes in TG or HDL over time, as presented in the Appendix (Section 16.2). Bempedoic acid resulted in decreased Apo-B during the trial (-8.1 to -10.8 mg/dL reduction from baseline (BL) at Week 52 over placebo), however, this degree of change is unlikely to significantly alter CV risk beyond the anticipated effect due to LDL-C lowering. The Applicant presented evidence to demonstrate a sustained reduction in median hsCRP over placebo from baseline to Week 12 (-8.7% to -31.0%) and Week 52 (-7.6% to -14.8%). However, review of hsCRP change in the original units revealed a decline from median baseline of 1.5 to 1.6 to median 0.79 to 1.45 at Week 12 and median 1.25 to 1.44 at Week 52 (Figure 13). Because baseline and follow-up values are all considered within normal limits, clinical implication of these small changes is unclear. Additional details are provided in the Appendix (Section 16.2).

Figure 13. TG Percent Change From Baseline



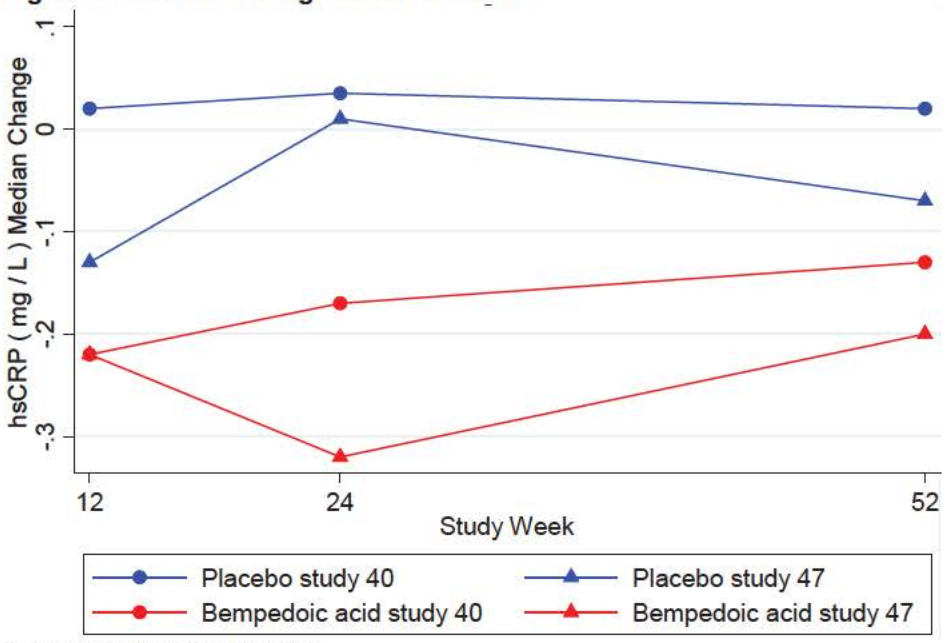
Source: FDA Statistical Reviewer
Abbreviations: TG, triglycerides

Figure 14. HDL Percent Change From Baseline



Source: FDA Statistical Reviewer
Abbreviations: HDL, high-density lipoprotein

Figure 15. hsCRP Change From Baseline



Source: FDA Statistical Reviewer
Abbreviations: hsCRP, high-sensitivity C-reactive protein

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Bempedoic acid underwent testing in a battery of studies consistent with the International Conference on Harmonisation (ICH)-M3(R2) guidance for industry. This included subchronic and chronic toxicology studies designed to identify and characterize potential clinical safety liabilities of bempedoic acid. Safety issues identified in animals included unexpected mortalities secondary to hypoglycemia (in rats and monkeys) and lactic acidosis (in rats) as well as synergistic toxicologic interaction between bempedoic acid and atorvastatin in monkeys.

Other toxicities of concern included liver toxicities (increases in LFTs, hepatocellular degeneration, hepatocellular necrosis, bile duct hyperplasia) in rodents and adaptive liver changes (increased liver weight, hepatocellular hypertrophy and vacuolation) in all tested species, anemia in rodents, and potential renal effects (increases in creatinine and BUN) in monkeys. Reduced red blood cell mass and changes in renal parameters (increase in creatinine and BUN) were ultimately observed clinically. Hypoglycemia, lactic acidosis and synergistic interaction between bempedoic acid and atorvastatin have not been observed in clinical trials, to date. A carcinogenicity study showed that, in addition to the hyperplasia and tumors expected for a weak PPARα agonist (e.g., pancreatic acinar cell and Leydig cell hyperplasia, and liver hepatocellular and thyroid follicular cell tumors), pancreatic islet cell tumors also occurred in male rats administered bempedoic acid for a lifetime.

Hypoglycemia and Lactic Acidosis

Administration of bempedoic acid at doses that result in high multiples of human exposures (i.e., ~17 times the clinical exposure at the human dose of 180 mg, based on AUC) resulted in deaths in rats and monkeys in repeat-dose toxicity studies within the first 2 weeks of treatment. Severely reduced blood glucose levels (rats and monkeys) and lactic acidosis (rats only) occurred within hours of dosing and preceded toxic effects at high doses leading, when untreated, to moribundity. Mechanisms leading to hypoglycemia could include lowered glucose production and/or increased glucose utilization coupled with reduced food consumption. Reduction of oxaloacetate (precursor for gluconeogenesis) secondary to pharmacologic inhibition of target ACL by bempedoic acid would be expected to reduce glucose synthesis.

Hypoglycemia with bempedoic acid monotherapy is not likely a concern for humans because it only occurred at high multiples of human exposure that are unlikely to occur clinically, are monitorable, and are reversible upon discontinuation of drug treatment and/or supplementation of a carbohydrate-rich diet. Similar sequala, including mortalities, hypoglycemia, and adverse liver toxicities were observed in monkeys coadministered clinically relevant doses of bempedoic acid and 10-fold the clinical dose of atorvastatin (based on BSA). In follow-up studies, a safety margin for the combination therapy was established at 3 times the clinical exposure at the human dose of 180 mg (based on AUC) for bempedoic acid and 1.3-fold the clinical dose at the maximum human dose of 80 mg (based on BSA) for atorvastatin. The mechanism of the toxicologic interactions between bempedoic acid and atorvastatin is not known. See Section 7.7.11.

Reduction in Red Blood Cell Mass

Minimal to mild reductions (5% to 17%) in red blood cell (RBC) mass (small decreases in erythrocytes, hemoglobin (Hgb), and hematocrit (Hct) levels) were observed in the 6-month rat study at ≥10 mg/kg/day. This is below the clinical exposure at the human dose of 180 mg, based on AUC. Lower RBC parameters were apparent in rats across all treatment durations; nevertheless, similar effects were absent in monkeys treated with bempedoic acid up to 13 times the clinical exposure at the human dose of 180 mg for 52 weeks. The cause of reduced RBC mass in rats is not known, as there was no correlative change observed in the bone marrow, spleen, or other organs in the pivotal studies.

Changes in Renal Clinical Chemistry Parameters

Dose-dependent increases in creatinine up to 62% were noted at doses ≥20 mg/kg/day (2 times the clinical exposure at the human dose of 180 mg, based on AUC) in the 52-week monkey study. No correlative changes in urine parameters and no histologic changes were associated with higher creatinine values in these animals. In the 26-week rat study, minimal to mild non-adverse brown tubular pigment (cortex) that were not iron reactive were observed at doses ≥10 mg/kg/day (below the systemic exposure at the human dose of 180 mg, based on AUC). The Applicant associated the increases in plasma creatinine levels to bempedoic acid–mediated inhibition of OAT2 (IC_{50} ~7× total C_{max} at the human dose of 180 mg), renal transporter of uric acid and creatinine.

Liver Toxicities

In the 26-week rat toxicity study, bempedoic acid caused dose-related increases in absolute and relative liver weights (23% to 154%) with correlative centrilobular to panlobular hepatocellular hypertrophy at all tested doses ≥10 mg/kg/day. This level (i.e.,10 mg/kg/day) of exposure in rats is below the clinical exposure at the human dose of 180 mg, based on AUC. In addition, LFTs (ALP, ALT, GGT) and total bilirubin were elevated in rats, which correlated with minimal to severe hepatocyte necrosis, subcapsular necrosis, and bile duct hyperplasia (predominantly noted in high-dose 60 mg/kg/day animals). Similar pathologies were noted in mice.

In the 52-week monkey toxicity study, histological change in liver was limited to periportal or diffuse vacuolation consistent with positive staining Oil Red O (lipids) at ≥20 mg/kg/day. This dose (i.e., 20 mg/kg/day) is 2 times the clinical exposure at the human dose of 180 mg, based on AUC. The liver changes were likely related to PPARα–mediated liver peroxisomal responses as evidenced by increases in the number of peroxisomes and induction of peroxisomal enzymes by transmission electron microscopy and biochemical analysis, respectively. In contrast to primates (i.e., monkeys and humans), rodents are hypersensitive to peroxisomal proliferative responses to PPARα agonists due to biological differences downstream of PPARα activation and therefore rodents overpredict human risk. The liver findings in monkeys are not unexpected, and monkeys are considered more relevant surrogates to predict human risk, compared to rodents.

Carcinogenic Potential of Bempedoic Acid

In the 2-year carcinogenicity study in mice, bempedoic acid caused statistically significant increases in the incidences of liver hepatocellular adenomas, hepatocellular carcinomas, and

hepatocellular adenomas combined with carcinomas in male mice at 75 and 150 mg/kg/day. This is ≥0.8 times the clinical exposure at the human dose of 180 mg, based on AUC.

In the 2-year rat carcinogenicity study, the incidences of hepatocellular adenomas, hepatocellular adenomas combined with carcinomas, thyroid follicular cell adenomas, follicular cell adenomas combined with carcinomas, and pancreas islet cell adenomas combined with carcinomas were statistical increased in male rats at 30 mg/kg/day. This is 1.4 times the clinical exposure at the human dose of 180 mg, based on AUC.

The liver and thyroid tumors are likely secondary to PPARα-mediated excessive hepatic peroxisomal proliferation and increased metabolism of thyroid hormones, respectively, and these tumors are considered unlikely to translate to human risk. The cause and human relevance of pancreas tumor findings in male rats is unclear. Refer to Section 7.7.10.

In conclusion, safety margins established from the 26-week rat and 52-week monkey studies support the proposed 180 mg/day dose of bempedoic acid and correspond to at least <1 and 13 times the clinical exposure at the human dose of 180 mg, respectively, based on AUC exposures at the nonclinical no observed adverse effect levels (NOAELs). The low safety margin in rodent studies is due to dose-limiting, rodent-specific PPARα-related effects that occurred at low multiples of clinical exposures. The monkey is considered more representative of the potential human responses than rodents for PPARα-mediated effects.

Table 18. Bempedoic Acid Safety Margins

Study	NOAEL (mg/kg)	Nonclinical Exposure (µg.hr/mL)	Safety Margins[1] (multiples)	Basis for NOAEL
3-month mouse	<100	438	<1.3	Adverse liver toxicities (hepatocellular degeneration, cytoplasmic alteration and ≥49% increases in liver weight) in mice treated at the lowest dose (100 mg/kg/day) tested.
6-month rat	10	58.5	<1	Adverse liver hepatocyte necrosis and ≥93% increases in liver weight in animals treated at ≥30 mg/kg/day.
12-month monkey	60	4483	13	Absence of adverse and frank toxicity at the highest dose (60 mg/kg/day) tested.

Source: Nonclinical Reviewer
[1] Exposure multiples were based on population pharmacokinetics analysis from phase 3 trials in which the maximum clinical dose resulted in systemic geometric mean combined ETC-1002 and ESP15228 exposures (AUC_{0-24hr}) of 340 µg.hr/mL.
Abbreviations: NOAEL, no observed adverse effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The following potential safety risks were reviewed based on information known about the statin drug class, which acts on the same cholesterol biosynthesis pathway as bempedoic acid.

- Myopathy and rhabdomyolysis
- Elevated liver enzymes
- Increases in fasting plasma glucose (FPG) and HbA1c

Common Risks Associated With Bempedoic Acid and Statins

Myopathy

- Two possible cases of drug-induced myopathy were observed in bempedoic acid–treated patients (0.08%) versus none in placebo patients. Neither case can be directly attributed to bempedoic acid (Table 19). One case was confounded by trauma and concomitant medications, and the second case resolved without drug discontinuation. One additional patient experienced other MSK symptoms (muscle spasm and pain in extremity) consistent with pre-exposure symptoms.
- CK elevations >5x ULN occurred in 1.0% to 1.2% of bempedoic acid patients versus 0.0% to 0.8% in placebo (high CV risk pool: bioavailability (BA) 1.2% versus PBO 0.8%; no/low statin pool: BA 1.0% versus PBO 0.0%). See Section 7.6.6 for laboratory findings.
- CK elevations >10x ULN occurred in 0.2% to 0.4% of bempedoic acid patients compared to 0.0% to 0.2% of placebo patients (high CV risk pool: BA 0.4% versus PBO 0.2%; no/low statin pool: BA 0.2% versus PBO 0.0%).

Hepatic enzyme elevations

- Isolated ALT/AST elevations >3x ULN were observed, but there was no evidence of drug-induced liver injury. See Section 7.6.6 for laboratory findings.

FPG and HbA1c

- No increases in FPG or HbA1c were observed with bempedoic acid exposure.

Table 19. Patients With CK >10x ULN or Reported TEAEs of Myopathy/Rhabdomyolysis/Myositis, Safety Population, High CV Risk Pool (Trials 040 and 047) and No/Low Statin Pool (Trials 046 and 048)

Arm USUBJID	Age/Sex Statin/Intensity Baseline eGFR	CK Value/Day Narrative[1] Conclusion: Drug-Induced Myopathy, Rhabdo, or Myositis?
Bempedoic acid (b) (6)	75 F Simvastatin moderate (40 mg) 30 to <60	CK 11,000 / Day 30 CK 11,000 / Day 35 Fall on Day 23 with moderate muscle strain (left hamstring and bilateral shoulders). On Day 30, 7 days postfall, CK 11,000 (protocol-driven lab testing). Pain in bilateral thighs with difficulty ambulating on Day 33 and increased BUN/Cr on Day 35 (42/1.6). Hospitalized on Day 36 for IVF. Discharged Day 38 with downtrending labs, resolved by Day 56. Bempedoic acid and simvastatin discontinued without rechallenge. Conclusion: possible drug-induced rhabdomyolysis (etiology: fall versus drug)
Bempedoic acid (b) (6)	52 M Rosuvastatin low, ezetimibe 60 to <90	CK 3366 / Day 183 CK 327 / Day 186 Intermittent stabbing pain in leg and arm (moderate severity, reported as “pain in extremity”) on Day 126 with subsequent CK elevation >10x ULN on Day 183 (57 days later). Pain in extremity ongoing at time of CK elevation. CK elevation resolved at Day 261 without drug discontinuation. Other notable events: tendon rupture / Day 345. Conclusion: possible drug-induced myopathy (resolution without drug dechallenge)
Bempedoic acid (b) (6)	62 M Atorvastatin moderate (20 mg) 60 to <90	CK 528 / Day 166 CK 367 / Day 251 CK 712 / Day 363 History of muscle spasms beginning in (b) (6) and ongoing at time of trial enrollment. Myalgia or muscle spasms reported on Days 61, 75, 114, 131, and 144. Mild CK elevation <3x ULN noted at Day 166. Subsequently evaluated for possible autoimmune myopathy; ANA and dsDNA positive on Day 187; no muscle biopsy for definitive diagnosis performed. Remained on bempedoic acid; no dechallenge/rechallenge. Conclusion: unlikely (symptoms consistent with those experienced predrug exposure)
Bempedoic acid (b) (6)	78 M Atorvastatin high (40 mg) 30 to <60	CK 577 / Day 252 Moderate adverse event of “myositis” reported on Day 252; appears to be solely based on CK elevation, no symptoms reported. Drug held temporarily for 36 days, then bempedoic acid resumed without issue. Conclusion: no

Arm USUBJID	Age/Sex Statin/Intensity Baseline eGFR	CK Value/Day Narrative[1] Conclusion: Drug-Induced Myopathy, Rhabdo, or Myositis?
Bempedoic acid (b) (6)	60 M Atorvastatin high 60 to <90	CK 3759 / Day 30 Asymptomatic Conclusion: no
Bempedoic acid (b) (6)	55 M Rosuvastatin high 60 to <90	CK 2896 / Day 5 Asymptomatic Conclusion: no
Bempedoic acid (b) (6)	68 M Atorvastatin high 60 to <90	CK 5043 / Day 169 Asymptomatic Conclusion: no
Bempedoic acid (b) (6)	71 M Atorvastatin high 60 to <90	CK 4,933 / Day 174 Asymptomatic Conclusion: no
Bempedoic acid (b) (6)	46 M Other low, ezetimibe 60 to <90	CK 4,230 / Day 29 CK 11,000 / Day 85 CK 4,895 / Day 89 Asymptomatic Other lab derangements: ALT/AST increased / Day 29 Conclusion: no
Bempedoic acid (b) (6)	64 M Atorvastatin high 60 to <90	CK 8,947 / Day 29 Asymptomatic Conclusion: no
Bempedoic acid (b) (6)	46 M None 60 to <90	CK 2,580 / Day 87 Asymptomatic Conclusion: no
Bempedoic acid (b) (6)	79 M Atorvastatin high 30 to >60	CK 103 / Day 90 CK 104 / Day 169 “Myopathy” (verbatim: cervical myopathy) and “nerve compression” (verbatim: numbness due to trapped nerve in neck) reported on Day 154. Conclusion: no
Placebo (b) (6)	46 M Rosuvastatin high 60 to <90	CK 4,088 / Day 53 Asymptomatic Conclusion: no

Arm USUBJID	Age/Sex Statin/Intensity Baseline eGFR	CK Value/Day Narrative[1] Conclusion: Drug-Induced Myopathy, Rhabdo, or Myositis?
Placebo (b) (6)	64 M Atorvastatin high ≥90	CK 3,414 / Day 31 Asymptomatic Other lab derangements: AST increased, creatinine increased / Day 31 **Conclusion:** no

Source: adlbchem.xpt, adae.xpt, adlburin.xpt; Software: JMP
[1] Based on review of MedDRA preferred terms and patient narratives
[2] Trial protocols modified to exclude patients taking simvastatin ≥40 mg after this case
Abbreviations: ALT. alanine aminotransferase; ANA, antinuclear ant bodies; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; Cr, creatinine; CV, cardiovascular; dsDNA, double-stranded DNA; IVF, intravenous fluid; TEAE, treatment-emergent adverse event; ULN, upper limit of normal

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Bempedoic acid is not approved or marketed in the United States or worldwide.

7.4. FDA Approach to Safety Review

For this review, the safety population was defined as randomized patients who received at least one dose of study drug. Patients were analyzed according to the actual treatment received. Patients from Trials 1002-040 and 1002-047 were pooled based on similarities in population, background therapy, and trial duration; in this review, they are referred to as the "high CV risk pool." Similarly, patients from Trials 1002-046 and 1002-048 were pooled and referred to in this review as the "no/low statin pool."

The Division did not agree with the Applicant's definition of treatment-emergent adverse events (TEAEs), which excluded AEs that occurred during the trial period but more than 30 days after drug discontinuation. Apart from Trial 048, a greater proportion of bempedoic acid–treated patients discontinued drug than placebo-treated patients. The Applicant's analysis approach introduced ascertainment bias in which collected safety data were more likely to be included for placebo-treated patients (who remain on drug) than for bempedoic acid–treated patients. For this review, all AEs that occurred after the first dose of drug and during the trial period were included in analyses.

Several adverse events were reclassified based upon review of verbatim to preferred term mapping (Appendix, Section 17.1.5). In general, reclassification decisions were meant to capture an adverse event's underlying etiology or to improve specificity. For example, "back pain due to fall" would be reclassified from "back pain" to "fall" or "bacteria in urine" would be reclassified from "bacterial test positive" to "bacteriuria." Generally, reclassification decisions did not significantly impact AE incidence. Additionally, adverse event terms that were considered to reflect the same clinical event were combined to avoid underestimation of incidence (Appendix, Section 17.1.5.2).

7.5. Adequacy of Clinical Safety Database

Total patient exposures were consistent with ICH guidelines and were sufficient for safety assessment of this chronically administered drug.

Table 20. Duration of Exposure, Safety Population, Trials 040, 046, 047, and 048

Parameter	Bempedoic Acid 180 mg N=2425	Placebo N=1198
Duration of treatment (weeks)		
Mean (SD)	39.4 (18.1)	41.3 (16.8)
Median (min, max)	51.7 (0.1, 76.9)	51.9 (0.1, 57.6)
Patients treated, by duration, n (%)		
Any duration (at least one dose)	2424 (100.0)	1197 (99.9)
<1 month1	96 (4.0)	40 (3.3)
≥1 month	2329 (96.0)	1157 (96.6)
≥3 months	2009 (82.8)	1039 (86.7)
≥6 months	1661 (68.5)	875 (73.0)
≥12 months2	590 (24.3)	317 (26.5)

Source: ADSL; Software: JMP
[1] 1 month =30 days
[2] 12 months =365 days
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

Table 21. Duration of Exposure, Safety Population, Trial 050[1]

Parameter	Bempedoic Acid 180 mg N=1462
Duration of treatment (weeks)	
Mean (SD)	80.1 (28.4)
Median (min, max)	89.6 (0.1, 132.0)
Patients treated, by duration, n (%)	
Any duration (at least one dose)	1462 (100.0)
<1 month2	6 (0.4)
≥1 month	1456 (99.6)
≥3 months	1445 (98.8)
≥6 months	1435 (98.2)
≥12 months3	1099 (75.2)

Source: ADSL; Software: JMP
[1] Trial 050 is an OLE that rolled over patients from Trial 040. For patients on bempedoic acid in Trial 040, total exposure time is accounted for (exposure in Trial 040 + exposure in Trial 050).
[2] 1 month =30 days
[3] 12 months =365 days
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

7.6.1. Overall Adverse Event Summary

In all trials, a slightly higher proportion of patients treated with bempedoic acid experienced at least one serious adverse event compared to placebo-treated patients. Additionally, a higher proportion of bempedoic acid–treated patients discontinued or paused treatment due to an adverse event compared to placebo-treated patients.

In the no/low statin pool, a higher proportion of bempedoic acid–treated patients experienced at least one TEAE compared to placebo patients. The proportion of patients who experienced at least one TEAE was similar between treatment arms in the high CV risk pool.

Table 22. Overview of Adverse Events,[1] Safety Population, High CV Risk Pool, Trials 040 and 047, 52 Weeks

Event	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Risk Difference (95% CI)
Any AE	1533 (76.3)	766 (76.7)	-0.4 (-3.6, 2.8)
Moderate or severe AEs (Grade 3–5)[2]	1081 (53.8)	519 (52.0)	1.9 (-1.9, 5.6)
SAE	322 (16.0)	152 (15.2)	0.8 (-1.9, 3.6)
SAEs with fatal outcome[3]	18 (0.9)	4 (0.4)	0.5 (-0.1, 1.1)
AE leading to discontinuation of study drug	219 (10.9)	75 (7.5)	3.4 (1.3, 5.5)
AE leading to interruption of study drug	244 (12.1)	97 (9.7)	2.4 (0.1, 4.8)

Source: ADAE; Software: JMP
[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug
[2] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; Severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up
[3] Does not include 11 deaths that were not associated with SAEs (7 deaths in bempedoic acid and 4 deaths in placebo
Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; CV, cardiovascular; N, number of subjects in group; n, number of subjects with at least one event

Table 23. Overview of Adverse Events,[1] Safety Population, No/Low Statin Pool, Trials 046 and 048, 12 to 24 Weeks

Event	Bempedoic Acid N=415 n (%)	Placebo N=198 n (%)	Risk Difference (95% CI)
Any AE	238 (57.3)	102 (51.5)	5.8 (-2.6, 14.3)
Moderate or severe AEs (Grade 3–5)[2]	120 (28.9)	54 (27.3)	1.6 (-5.9, 9.2)
SAE	19 (4.6)	7 (3.5)	1.0 (-2.2, 4.3)
SAEs with fatal outcome	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
AE leading to discontinuation of study drug	54 (13.0)	18 (9.1)	3.9 (-1.2, 9.1)
AE leading to interruption of study drug	22 (5.3)	9 (4.5)	0.8 (-2.9, 4.4)

Source: ADAE; Software: JMP
[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug
[2] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; Severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up
Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with at least one event

7.6.2. Deaths

In the high CV risk pool, 25 deaths (1.2%) were reported amongst patients treated with bempedoic acid compared to eight deaths (0.8%) amongst placebo-treated patients. No deaths occurred in the no/low statin, short-term trials.

The death imbalance was primarily driven by malignancy-associated deaths that occurred ≥30 days after the last dose of bempedoic acid. Additional death description and analyses are presented in Section 7.7.1.

Nine additional deaths were reported in the ongoing, uncontrolled OLE trial; however, interpretation of safety findings in the absence of placebo control is challenging.

Table 24. Deaths in Safety Population, High CV Risk Pool, Trials 040 and 047, 52 Weeks

Deaths	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)
Total deaths	25 (1.2)	8 (0.8)
Cardiovascular	12 (0.6)	5 (0.5)
Malignancy	9 (0.4)	1 (0.1)
Other	4 (0.2)	2 (0.2)
Within 30 days of last dose	14 (0.7)	4 (0.4)
Cardiovascular	11 (0.5)	3 (0.3)
Malignancy	1 (0.0)	1 (0.1)
Other	3 (0.1)	1 (0.1)
Beyond 30 days of last dose	11 (0.5)	4 (0.4)
Cardiovascular	1 (0.0)	2 (0.2)
Malignancy	8 (0.4)	0 (0.0)
Other	1 (0.0)	1 (0.1)

Source: ADAE; Software: JMP
Abbreviations: CV, cardiovascular; N, number of subjects in group; n, number of deaths

Table 25. Deaths in Safety Population, High CV Risk Open-Label Extension, Trial 050, Ongoing

Deaths	Bempedoic Acid N=1462 n (%)
Total deaths	9 (0.6)
Cardiovascular	4 (0.3)
Malignancy	2 (0.1)
Other	3 (0.2)
Within 30 days of last dose	7 (0.5)
Cardiovascular	4 (0.3)
Malignancy	0 (0.0)
Other	3 (0.2)
Beyond 30 days of last dose	2 (0.1)
Cardiovascular	0 (0.0)
Malignancy	2 (0.1)
Other	0 (0.0)

Source: ADAE; Software: JMP
Abbreviations: CV, cardiovascular; N, number of subjects in group; n, number of deaths

7.6.3. Serious Adverse Events

Overall, a small imbalance in patients experiencing at least one serious adverse event (SAE) was observed between bempedoic acid– and placebo-treated patients in both trial populations. The imbalance was largely driven by small imbalances (i.e., one or two patients with events in the bempedoic acid arm versus none in placebo) for multiple, infrequent SAEs, and without an identifiable clinical pattern.

In the high CV risk patient pool, more drug-treated patients experienced angina, atrial fibrillation, pneumonia, cardiac failure, and tendon rupture than placebo. In the no/low statin, primary and secondary prevention pool, more drug-treated patients experienced unstable angina, CAD, and stroke.

Additional analyses on cardiovascular risk and tendon rupture are presented in Sections 7.7.1.2 and 7.7.2.

Table 26. Serious Adverse Events by Descending Difference (>0.1%) Order, Safety Population, High CV Risk Pool, Trials 040 and 047

Adverse Event[1,2]	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Risk Difference (95% CI)
Patients with at least one SAE	322 (16.0)	152 (15.2)	0.8 (-1.9, 3.6)
Angina pectoris	18 (0.9)	5 (0.5)	0.4 (-0.2, 1.0)
Atrial fibrillation	11 (0.5)	2 (0.2)	0.3 (-0.1, 0.8)
Cardiac failure congestive[3]	10 (0.5)	2 (0.2)	0.3 (-0.1, 0.7)
Pneumonia	8 (0.4)	2 (0.2)	0.2 (-0.2, 0.6)
Tendon rupture	4 (0.2)	0 (0.0)	0.2 (0.0, 0.4)
Diverticulitis	5 (0.2)	1 (0.1)	0.1 (-0.1, 0.4)
Urinary tract infection	5 (0.2)	1 (0.1)	0.1 (-0.1, 0.4)
Benign prostatic hyperplasia	4 (0.2)	1 (0.1)	0.1 (-0.2, 0.4)
Gastritis	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Cholecystitis	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Erysipelas	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Hyperkalaemia	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Back pain	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Lung neoplasm malignant	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Bradycardia	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Pericarditis	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Sinus node dysfunction	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Supraventricular tachycardia	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Pancreatitis acute	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Clostridium difficile infection	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Gastroenteritis	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Influenza	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Pyelonephritis	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Facial bones fracture	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Radius fracture	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Adenocarcinoma of colon	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Bladder neoplasm	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Brain oedema	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)

Adverse Event[1,2]	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Risk Difference (95% CI)
Carotid artery disease	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Uterine prolapse	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Asthma	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Sleep apnoea syndrome	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Peripheral ischaemia	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)

Source: Reviewer's analysis [adsl.xpt and addd.xpt; Software: Python]
[1] Coded as MedDRA preferred terms
[2] Terms included are those that occurred more often in the treatment than comparator group.
[3] Includes cardiac failure congestive and cardiac failure chronic
Abbreviations: CI, confidence interval; CV, cardiovascular; N, number of subjects in group; n, number of subjects with adverse event; SAE, serious adverse event

Table 27. Serious Adverse Events by Descending Difference (>0.1%) Order, Safety Population, No/Low Statin Pool, Trials 046 and 048

Adverse Event[1,2]	Bempedoic Acid N=415 n (%)	Placebo N=198 n (%)	Risk Difference (95% CI)
Patients with at least one SAE	19 (4.6)	7 (3.5)	1.0 (-2.2, 4.3)
Angina unstable	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Coronary artery disease	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Stroke[3]	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Angina pectoris	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Myocardial infarction	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Corneal lesion	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Colitis	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Intestinal obstruction	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Non-cardiac chest pain	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Bronchitis	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Lower respiratory tract infection bacterial	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Staphylococcal infection	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Urinary tract infection	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Osteoarthritis	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Hepatic cancer	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Myeloproliferative neoplasm	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Hypoxic-ischaemic encephalopathy	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Seizure	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Syncope	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Dysuria	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Pneumonia aspiration	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Respiratory failure	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)

Source: Reviewer's analysis [adsl.xpt and addd.xpt; Software: Python]
[1] Coded as MedDRA preferred terms
[2] Terms included are those that occurred more often in the treatment than comparator group.
[3] Includes cerebrovascular accident and ischemic stroke
Abbreviations: CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event; SAE, serious adverse event

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

More bempedoic acid patients than placebo patients discontinued drug due to an adverse event. Across all trials, the most common reasons for drug discontinuation were diarrhea, musculoskeletal symptoms (such as pain in extremity or muscle spasms), elevated liver enzymes, other gastrointestinal symptoms (such as abdominal pain or nausea), and headache. An adverse reason for discontinuation that was unique to high CV risk patients was myocardial infarction, 0.3% versus 0.1%, which is not unexpected in this patient population. Unique reasons for discontinuation (only one reason listed per patient) among patients on no or low background statin were dizziness, arthralgias, and back pain.

Table 28. Adverse Events Leading to Discontinuation by Descending Difference (>0.1%) Order, Safety Population, High CV Risk Pool, Trials 040 and 047

Adverse Event[1,2]	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Risk Difference (95% CI)
Patients with at least one AE leading to discontinuation	219 (10.9)	75 (7.5)	3.4 (1.3, 5.5)
Diarrhea[3]	10 (0.5)	1 (0.1)	0.4 (0.0, 0.8)
Pain in extremity	6 (0.3)	0 (0.0)	0.3 (0.1, 0.5)
Muscle spasms	11 (0.5)	3 (0.3)	0.2 (-0.2, 0.7)
Myocardial infarction	7 (0.3)	1 (0.1)	0.2 (-0.1, 0.6)
Elevated liver enzymes[4]	7 (0.3)	1 (0.1)	0.2 (-0.1, 0.6)
Abdominal pain[5]	6 (0.3)	1 (0.1)	0.2 (-0.1, 0.5)
Headache	9 (0.4)	3 (0.3)	0.1 (-0.3, 0.6)
Nausea	6 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)
Dyspnoea	5 (0.2)	1 (0.1)	0.1 (-0.1, 0.4)
Anaemia	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Gastroesophageal reflux disease	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Vomiting	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Musculoskeletal pain	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Angina unstable	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Visual impairment	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Blood uric acid increased	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
International normalised ratio increased	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Decreased appetite	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Hyperkalaemia	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Osteoarthritis	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Lung neoplasm malignant	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Prostate cancer	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Cough	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)

Source: Reviewer's analysis [adae.xpt; Software: Python]
[1] Coded as MedDRA preferred terms
[2] Terms included are those that occurred more often in the treatment than comparator group
[3] Includes diarrhea and frequent bowel movements
[4] Includes aspartate aminotransferase increased and alanine aminotransferase increased
[5] Includes abdominal pain upper and abdominal pain lower
Abbreviations: AE, adverse event; CI, confidence interval; CV, cardiovascular; N, number of subjects in group; n, number of subjects with adverse event

Table 29. Adverse Events Leading to Discontinuation by Descending Difference (>0.1%) Order, Safety Population, No/Low Statin Pool, Trials 046 and 048

Adverse Event[1,2]	Bempedoic Acid N=415 n (%)	Placebo N=198 n (%)	Risk Difference (95% CI)
Patients with at least one AE leading to discontinuation	54 (13.0)	18 (9.1)	3.9 (-1.2, 9.1)
Muscle spasms	7 (1.7)	0 (0.0)	1.7 (0.4, 2.9)
Pain in extremity	4 (1.0)	0 (0.0)	1.0 (0.0, 1.9)
Elevated liver enzymes[3]	4 (1.0)	0 (0.0)	1.0 (0.0, 1.9)
Diarrhoea[4]	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Dizziness	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Arthralgia	4 (1.0)	1 (0.5)	0.5 (-0.9, 1.8)
Confusional state[5]	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Back pain	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Headache	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Angina unstable	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Myocardial infarction	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Palpitations	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Ventricular extrasystoles	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Abdominal pain	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Dyspepsia	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Gastrooesophageal reflux disease	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Nausea	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Chest pain	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Myalgia	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Oedema	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Hepatic function abnormal	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Staphylococcal infection	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Blood creatine phosphokinase increased	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Limb discomfort	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Muscular weakness	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Hepatic cancer	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Dysgeusia	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Anxiety	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Nephrolithiasis	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Renal failure	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Breast tenderness	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Dyspnoea	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Pneumonia aspiration	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Pain of skin	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Petechiae	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Rash erythematous	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Rash generalized	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Hot flush	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)

Source: Reviewer's analysis [adae.xpt; Software: Python]
[1] Coded as MedDRA preferred terms
[2] Terms included are those that occurred more often in the treatment than comparator group
[3] Includes aspartate aminotransferase increased, alanine aminotransferase increased, and liver function test abnormal
[4] Includes diarrhea and frequent bowel movements
[5] Includes confusional state and disorientation
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

7.6.5. Treatment-Emergent Adverse Events

Bempedoic acid's safety profile was generally consistent across the high CV risk pool and the no/low statin pool. The most common adverse events occurring more frequently in the bempedoic acid arm than in the placebo arm were increases in uric acid and gout, MSK-related AEs (muscle spasms, pain in extremity, and general MSK pain), elevated liver enzymes, gastrointestinal side effects (dyspepsia, vomiting), and changes to renal lab parameters (increases in BUN/creatinine (Cr) or decreases in eGFR). An adverse event unique to the high CV risk pool was benign prostatic hyperplasia; detection of this in the high CV risk pool only likely reflects differences in trial duration, size, and patient demographics. The most common adverse events that were observed in the no/low statin pool only and occurred more frequently in bempedoic acid than in placebo were hypertension, dizziness, increased creatine phosphokinase, and unstable angina.

Although there was a reported difference of AEs of hypertension, there were no differences in measured blood pressure over time between arms in the Vital Signs data from any trial (Appendix, Section 17.1.2.), and there was no evidence to support an imbalance in cardiovascular disease (Risk Review Issue #1) between bempedoic acid and placebo in any trial.

Table 30. Adverse Events[1] Occurring at 0.5% Higher Frequency in Treatment Arm Than Comparator Arm, Safety Population, High CV Risk Pool, Trials 040 and 047

	Trial 040		Trial 047		Pooled[3]		
Preferred Term[2]	Bempedoic Acid N=1487 n (%)	Placebo, N=742 n (%)	Bempedoic Acid N=522 n (%)	Placebo N=257 n (%)	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Risk Difference (95% CI)
Increased uric acid[4]	34 (2.3)	5 (0.7)	36 (6.9)	6 (2.3)	70 (3.5)	11 (1.1)	2.4 (1.4, 3.4)
Muscle spasms	62 (4.2)	20 (2.7)	11 (2.1)	3 (1.2)	73 (3.6)	23 (2.3)	1.3 (0.1, 2.6)
Pain in extremity	50 (3.4)	16 (2.2)	11 (2.1)	1 (0.4)	61 (3.0)	17 (1.7)	1.3 (0.2, 2.4)
Elevated liver enzymes[5]	34 (2.3)	7 (0.9)	10 (1.9)	3 (1.2)	44 (2.2)	10 (1.0)	1.2 (0.3, 2.1)
Back pain	56 (3.8)	18 (2.4)	10 (1.9)	4 (1.6)	66 (3.3)	22 (2.2)	1.1 (-0.1, 2.3)
Vomiting	22 (1.5)	2 (0.3)	5 (1.0)	0 (0.)	27 (1.3)	2 (0.2)	1.1 (0.6, 1.7)
Gout[6]	19 (1.3)	2 (0.3)	12 (2.3)	2 (0.8)	31 (1.5)	4 (0.4)	1.0 (0.4, 1.7)
Changes to renal lab parameters[7]	19 (1.3)	3 (0.4)	8 (1.5)	1 (0.4)	27 (1.3)	4 (0.4)	0.9 (0.3, 1.6)
Anaemia	43 (2.9)	16 (2.2)	14 (2.7)	3 (1.2)	57 (2.8)	19 (1.9)	0.9 (-0.2, 2.1)
Renal insufficiency[8]	14 (0.9)	1 (0.1)	4 (0.8)	0 (0.0)	18 (0.9)	1 (0.1)	0.8 (0.3, 1.3)
Benign prostatic hyperplasia	13 (0.9)	3 (0.4)	5 (1.0)	0 (0.0)	18 (0.9)	3 (0.3)	0.6 (0.1, 1.1)
Atrial fibrillation	23 (1.5)	9 (1.2)	11 (2.1)	2 (0.8)	34 (1.7)	11 (1.1)	0.6 (-0.3, 1.4)
Upper respiratory tract infection	72 (4.8)	31 (4.2)	19 (3.6)	9 (3.5)	91 (4.5)	40 (4.0)	0.5 (-1.0, 2.0)
Bronchitis	53 (3.6)	19 (2.6)	7 (1.3)	6 (2.3)	60 (3.0)	25 (2.5)	0.5 (-0.7, 1.7)
Abdominal pain or discomfort[9]	35 (2.4)	10 (1.3)	4 (0.8)	4 (1.6)	39 (1.9)	14 (1.4)	0.5 (-0.4, 1.5)

Source: Reviewer's analysis [adae.xpt; Software: Python]
[1] Treatment-emergent adverse event defined as any adverse event that occurred after the first dose of drug
[2] Coded as MedDRA preferred terms, terms included are those that occurred more often (≥0.3%) in the treatment than comparator group.
[3] Pooled phase 3 population or ISS
[4] Includes blood uric acid increased and hyperuricemia
[5] Includes aspartate aminotransferase increased, alanine aminotransferase increased, hepatic enzyme increased, liver function test increased, liver function test abnormal
[6] Includes gout and gouty arthritis
[7] Includes blood creatinine increased and glomerular filtration rate decreased
[8] Coded as renal failure by MedDRA preferred terms, however, review of verbatim coding indicates events were related to renal insufficiency (primarily increases in BUN or creatinine)
[9] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort
Abbreviations: CI, confidence interval; CV, cardiovascular; N, number of subjects in group; n, number of subjects with adverse event

Table 31. Adverse Events[1] Occurring at 0.5% Higher Frequency in Treatment Arm Than Comparator Arm, Safety Population, No/Low Statin Pool, Trials 046 and 048

	Trial 046		Trial 048		Pooled[4]		
Preferred Term[2,3]	Bempedoic Acid, N=234 n (%)	Placebo, N=111 n (%)	Bempedoic Acid N=181 n (%)	Placebo, N=87 n (%)	Bempedoic Acid N=415 n (%)	Placebo, N=198 n (%)	Risk Difference (95% CI)
Increased uric acid[5]	6 (2.6)	0 (0.0)	15 (8.3)	2 (2.3)	21 (5.1)	2 (1.0)	4.1 (1.5, 6.6)
Elevated liver enzymes[6]	3 (1.3)	0 (0.0)	13 (7.2)	0 (0.0)	16 (3.9)	0 (0.0)	3.9 (2.0, 5.7)
Hypertension[7]	12 (5.1)	2 (1.8)	3 (1.7)	1 (1.1)	15 (3.6)	3 (1.5)	2.1 (-0.4, 4.6)
Dizziness	7 (3.0)	0 (0.0)	3 (1.7)	1 (1.1)	10 (2.4)	1 (0.5)	1.9 (0.1, 3.7)
Blood creatine phosphokinase increased	5 (2.1)	0 (0.0)	3 (1.7)	0 (0.0)	8 (1.9)	0 (0.0)	1.9 (0.6, 3.3)
Sinusitis	4 (1.7)	1 (0.9)	5 (2.8)	0 (0.0)	9 (2.2)	1 (0.5)	1.7 (-0.1, 3.4)
Arthralgia	14 (6.0)	5 (4.5)	3 (1.7)	0 (0.0)	17 (4.1)	5 (2.5)	1.6 (-1.3, 4.5)
Dyspepsia	5 (2.1)	0 (0.0)	1 (0.6)	0 (0.0)	6 (1.4)	0 (0.0)	1.4 (0.3, 2.6)
Chest pain or discomfort[8]	6 (2.6)	1 (0.9)	2 (1.1)	0 (0.0)	8 (1.9)	1 (0.5)	1.4 (-0.2, 3.1)
Musculoskeletal pain	3 (1.3)	0 (0.0)	2 (1.1)	0 (0.0)	5 (1.2)	0 (0.0)	1.2 (0.2, 2.3)
Pain in extremity	12 (5.1)	4 (3.6)	1 (0.6)	0 (0.0)	13 (3.1)	4 (2.0)	1.1 (-1.5, 3.7)
Angina unstable	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)	0 (0.0)	1.0 (0.0, 1.9)
Changes to renal lab parameters[9]	0 (0.0)	0 (0.0)	4 (2.2)	0 (0.0)	4 (1.0)	0 (0.0)	1.0 (0.0, 1.9)
Nausea	4 (1.7)	3 (2.7)	5 (2.8)	0 (0.0)	9 (2.2)	3 (1.5)	0.7 (-1.6, 2.9)
Anaemia	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Coronary artery disease	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Muscle strain	1 (0.4)	0 (0.0)	2 (1.1)	0 (0.0)	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Hypercalcaemia	0 (0.0)	0 (0.0)	3 (1.7)	0 (0.0)	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Anxiety	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Pruritus generalized	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)
Abdominal pain	2 (0.9)	1 (0.9)	2 (1.1)	0 (0.0)	4 (1.0)	1 (0.5)	0.5 (-0.9, 1.8)
Influenza	4 (1.7)	0 (0.0)	0 (0.0)	1 (1.1)	4 (1.0)	1 (0.5)	0.5 (-0.9, 1.8)
Gout	4 (1.7)	1 (0.9)	0 (0.0)	0 (0.0)	4 (1.0)	1 (0.5)	0.5 (-0.9, 1.8)
Renal failure	2 (0.9)	0 (0.0)	2 (1.1)	1 (1.1)	4 (1.0)	1 (0.5)	0.5 (-0.9, 1.8)
Angina pectoris	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Gastritis	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Mouth ulceration	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Cystitis	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Tooth abscess	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Viral upper respiratory tract infection	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Neutrophil count decreased	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Dehydration	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Hyponatraemia	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)

	Trial 046		Trial 048		Pooled[4]		
Preferred Term[2,3]	Bempedoic Acid, N=234 n (%)	Placebo, N=111 n (%)	Bempedoic Acid N=181 n (%)	Placebo, N=87 n (%)	Bempedoic Acid N=415 n (%)	Placebo, N=198 n (%)	Risk Difference (95% CI)
Impaired fasting glucose	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Fibromyalgia	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Melanocytic naevus	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Dysgeusia	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Hypoaesthesia	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Renal impairment	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Dyspnoea exertional	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Sleep apnoea syndrome	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Hyperhidrosis	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)
Hot flush	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.5)	0 (0.0)	0.5 (-0.2, 1.1)

Source: Reviewer's analysis [adae.xpt; Software: Python]
[1] Treatment-emergent adverse event defined as any adverse event that occurred after the first dose of drug
[2] Coded as MedDRA preferred terms
[3] Terms included are those that occurred more often (0.5%) in the treatment than comparator group.
[4] Pooled phase 3 population or ISS
[5] Includes blood uric acid increased and hyperuricemia
[6] Includes aspartate aminotransferase increased, alanine aminotransferase increased, hepatic enzyme increased, and liver function test increased
[7] Includes hypertension and blood pressure increased
[8] Includes chest pain and chest discomfort
[9] Includes blood creatinine increased and glomerular filtration rate decreased
Abbreviations: CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

7.6.6. Laboratory Findings

The phase 3 trials identified associations between bempedoic acid use and changes in various laboratory parameters. Isolated elevations in CK above various thresholds (e.g., >ULN, >5x ULN, >10x ULN) occurred at slightly higher incidences in the bempedoic acid arms compared to the placebo arms, regardless of background statin use. Isolated AST/ALT elevations (>3x ULN, >5x ULN) occurred at similar incidences between treatment arms in the high-risk pool, and at slightly higher incidences in the bempedoic acid group compared to placebo in the no/low statin pool. Effects on hematology parameters included decreases in hemoglobin and total WBC and minimal-mild increases in platelet counts in all trials; these changes were generally reversible with drug discontinuation. Additionally, changes to renal lab parameters (increased BUN and creatinine, decreased eGFR) were observed more frequently with across all trials. Specific changes of clinical interest are further discussed in Sections 7.7.3, 7.7.5, 7.7.6, 7.7.7, 7.7.8, and 7.7.9.

Table 32. Patients Meeting Laboratory Abnormality Criteria, From Baseline Through Week 52 (High CV Risk Pool) and Week 12 to 24 (No/Low Statin Pool), Safety Population

	High CV Risk Pool		No/Low Statin Pool	
Laboratory Analysis	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Bempedoic Acid N=415 n (%)	Placebo N=198 n (%)
CK elevations (BL normal to FU high)	435 (21.7)	182 (18.2)	38 (9.2)	13 (6.6)
>3x-fold ULN	61 (3.0)	29 (2.9)	13 (3.1)	5 (2.5)
>5x-fold ULN	24 (1.2)	8 (0.8)	4 (1.0)	0 (0.0)
>10x-fold ULN	8 (0.4)	2 (0.2)	1 (0.2)	0 (0.0)
Hepatic enzyme elevations				
AST >3x-fold ULN	29 (1.4)	4 (0.4)	9 (2.2)	0 (0.0)
AST >5x-fold ULN	9 (0.4)	2 (0.2)	2 (0.5)	0 (0.0)
ALT >3x-fold ULN	7 (0.3)	3 (0.3)	4 (1.0)	0 (0.0)
ALT >5x-fold ULN	2 (0.1)	2 (0.2)	1 (0.2)	0 (0.0)
TB >2x-fold ULN	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Hemoglobin decrease				
≥2 g/dL from baseline	160 (8.0)	37 (3.7)	14 (3.4)	0 (0.0)
≥3 g/dL from baseline	35 (1.7)	13 (1.3)	6 (1.4)	0 (0.0)
≥5 g/dL from baseline	3 (0.1)	2 (0.2)	2 (0.5)	0 (0.0)
≥2 g/dL decline and < LLN	103 (5.1)	23 (2.3)	9 (2.2)	0 (0.0)
WBC decrease				
$<4\times10^9$/L and normal at baseline	180 (9.0)	67 (6.7)	31 (7.5)	7 (3.5)
Platelet increase				
Increase $>100\times10^9$/L from baseline	203 (10.1)	47 (4.7)	28 (6.7)	2 (1.0)
>2x-fold from baseline	12 (0.6)	2 (0.2)	2 (0.2)	0 (0.0)
$>500\times10^9$/L and normal at baseline	18 (0.9)	5 (0.5)	0 (0.0)	0 (0.0)
$>750\times10^9$/L and normal at baseline	2 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Creatinine increase				
>30% from baseline anytime	167 (8.3)	47 (4.7)	39 (9.4)	6 (3.0)
>30% from baseline by Week 4	40 (2.0)	6 (0.6)	18 (4.3)	1 (0.5)
>0.5 mg/dL from baseline	44 (2.2)	11 (1.1)	2 (0.5)	0 (0.0)
>1 mg/dL from baseline	7 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)

Laboratory Analysis	High CV Risk Pool		No/Low Statin Pool	
	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Bempedoic Acid N=415 n (%)	Placebo N=198 n (%)
BUN increase				
Normal baseline to > ULN	465 (23.1)	148 (14.8)	96 (23.1)	22 (11.1)
Normal baseline to >2x-fold increase	76 (3.8)	15 (1.5)	9 (2.2)	3 (1.5)
Normal baseline to >2x-fold increase and > ULN	46 (2.3)	10 (1.0)	1 (0.2)	2 (1.0)
eGFR decrease				
>30% from baseline	101 (5.0)	35 (3.5)	20 (4.8)	0 (0.0)
>50% from baseline	15 (0.7)	5 (0.5)	0 (0.0)	0 (0.0)
>60 at baseline and <30	1 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
>60 baseline and <15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; BUN, blood urea nitrogen; CK, creatine kinase; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FU, follow-up; LLN, lower limit of normal; N, number of subjects in treatment group; n, number of subjects who experienced the event; TB, total bilirubin; ULN, upper limit of normal; WBC, white blood cell

Table 33. Placebo-Adjusted Mean Change From Baseline in Selected Laboratory Parameters, Safety Population

Laboratory Analysis	High CV Risk Pool		No/Low Statin Pool	
	Trial 040 Bempedoic Acid N=1487	Trial 047 Bempedoic Acid N=522	Trial 046 Bempedoic Acid N=234	Trial 048 Bempedoic Acid N=181
Alkaline phosphatase (U/L)				
Week 4	-13.5	-12.3	-12.8	-8.3
Week 12	-14.1	-12.4	-12.2	-10.8
Week 24	-14.6	-11.2	-11.3	
Week 52	-13.5	-12.2		
Fasting plasma glucose (mg/dL)				
Week 4	-2.7	-2.9	1.9	0.5
Week 12	-1.4	-3.2	-1.4	-4.4
Week 24	-0.5	-3.7	-1.5	
Week 52	-2.0	-1.2		
HbA1c (%)				
Week 4				-0.1
Week 12	-0.1	-0.1	-0.1	0.0
Week 24		-0.1	-0.1	
Week 52	-0.1	0		
Uric acid (mg/dL)				
Week 4	0.8	0.7	0.9	0.5
Week 12	0.8	0.8	0.9	0.7
Week 24	0.8	0.8	0.8	
Week 52	0.8	0.5		
WBC (10^9/L)				
Week 4	-0.3	-0.2	-0.3	-0.5
Week 12	-0.3	0.0	-0.2	-0.4
Week 24	-0.3	-0.1	-0.1	
Week 52	-0.3	-0.1		

Laboratory Analysis	High CV Risk Pool		No/Low Statin Pool	
	Trial 040 Bempedoic Acid N=1487	Trial 047 Bempedoic Acid N=522	Trial 046 Bempedoic Acid N=234	Trial 048 Bempedoic Acid N=181
Platelets (10^9/L)				
Week 4	17.1	14.6	17.6	18.8
Week 12	19.3	15.3	17.9	25.4
Week 24	14.5	15.0	19.3	
Week 52	15.5	12.4		

Source: Reviewer's analysis
Abbreviations: CV, cardiovascular; HbA1c, hemoglobin A1c; N, number of subjects in treatment group; n, number of subjects who experienced the event; WBC, white blood cell

Table 34. Patients Meeting Urinalysis Abnormality Criteria[1], From Baseline Through Week 52, Trial 040[2]

Laboratory Analysis	Bempedoic Acid N=1487 n (%)	Placebo N=742 n (%)
Urine protein (mg/dL)	140 (9.4)	69 (9.3)
>300 mg/dL	0 (0.0)	1 (0.1)
>100 mg/dL	7 (0.5)	4 (0.5)
>30 mg/dL	34 (2.3)	25 (3.4)
Trace	130 (8.7)	57 (7.7)
Erythrocytes		
Cells (#/HPF)	119 (8.0)	65 (8.8)
Casts (#/LPF)	0 (0.0)	1 (0.1)
Tubular epithelial cells (#/HPF)		
Occasional	1 (<0.1)	0 (0.0)
Granular casts (#/LPF)	4 (0.3)	4 (0.5)
0 to 7	4 (0.3)	4 (0.5)
Uric acid crystals (#/LPF)		
Many	31 (2.1)	21 (2.8)
Moderate	12 (0.8)	6 (0.8)
Occasional	7 (0.5)	7 (0.9)
Few	9 (0.6)	5 (0.7)
Ketones (mg/dL)	24 (1.6)	17 (2.3)
>40	2 (0.1)	0 (0.0)
>15	3 (0.2)	5 (0.7)
Trace	19 (1.3)	13 (1.8)

Source: Reviewer's analysis [ad burin.xpt; Software: JMP]
[1] Who had normal urinalysis at baseline
[2] Urinalysis was only performed in Trial 040
Abbreviations: HPF, high-power field; LPF, low-power field; N, number of subjects in treatment group; n, number of subjects with event

7.7. Review Issues Relevant to Evaluation of Risk

7.7.1. Death Imbalance

Issue

Twenty-five deaths were observed in patients exposed to bempedoic acid compared to eight deaths in placebo-treated patients in the long-term, 52-week trials. The most common causes of death (COD) were cardiovascular and malignancy.

Conclusion

The overall imbalance in all-cause deaths between arms was primarily driven by malignancy-associated deaths that occurred >30 days after drug discontinuation. Observed imbalances in deaths were most likely due to chance. Review of the safety database—including exposure-adjusted mortality data, analyses of nonfatal adverse events, and information from case narratives (including latency to cancer diagnosis)—did not support an association between bempedoic acid exposure and mortality, CV harm, or malignancy risk.

Assessment

Additional analyses were performed to further evaluate evidence for CV harm or carcinogenicity risk with bempedoic acid exposure. The above conclusions are based on assessments shown in Sections 7.7.1.1, 7.7.1.2, and 7.7.1.3.

7.7.1.1. All-Cause Death Imbalance

Narratives were reviewed for COD. Most deaths occurred in Trial 040. In both trials, most patients died due to cardiovascular disease or malignancies, consistent with the demographics and baseline characteristics of enrolled population.

All-Cause Deaths

25 all-cause deaths observed in bempedoic acid-treated patients (16 expected based on 2:1 randomization)

25 bempedoic acid versus 8 placebo

- By trial
  - Trial 040, 17 versus 5
  - Trial 047, 8 versus 3
- By COD
  - Cardiovascular, 12 versus 5
  - Malignancy, 9 versus 1
  - Other, 4 versus 2
- By COD and trial
  - Cardiovascular, 12 versus 5
    - Trial 040, 8 versus 2

    - Trial 047, 4 versus 3
- Malignancy, 9 versus 1
    - Trial 040, 8 versus 1
    - Trial 047, 1 versus 0

Cardiovascular and malignancy risk were individually examined to further understand the mortality imbalance. Considering 2:1 randomization, there was no imbalance in "other" causes of death.

7.7.1.2. Cardiovascular Death Imbalance

Detailed reviews of death narratives and analyses of adverse events, vital signs, electrocardiograms (ECGs), and labs were performed to evaluate the potential for cardiovascular harm with bempedoic acid. Considering 2:1 randomization, there were only 2 additional cardiovascular deaths in bempedoic acid-treated patients than expected, and the imbalance was only observed in trial 040 (there was a slightly higher proportion of cardiovascular deaths in the placebo arm of trial 040).

Cardiovascular Deaths

12 cardiovascular deaths observed in bempedoic acid-treated patients (10 expected based on 2:1 randomization)

- Cardiovascular deaths, 12 versus 5
    - Trial 040, 8 versus 2
    - Trial 047, 4 versus 3

Nonfatal ASCVD or thrombotic events

Review of nonfatal AEs did not reveal any imbalance in MI (RD -0.5 [-1.3, 0.3]) or stroke (RD -0.1 [-0.6, 0.5]). Furthermore, there was no imbalance in 5-point MACE, 3-point MACE, noncoronary revascularization (Table 37), or other nonfatal ASCVD adverse events (Table 38). In fact, MACE trends favored bempedoic acid (higher rate in placebo) in both trials.

Evaluation for possible MOA

Although a minimal increase in platelets from baseline was observed with bempedoic acid exposure (mean increase of 14.6 to 25.4×10^9/L), this change is likely too small to confer additional risk. Moreover, there was no imbalance in patients with platelet counts $>750{,}000\times10^9$/L (0.0% versus 0.1%), the amount of thrombocytosis associated with increased risk for clotting events such as MI or stroke.

Table 35. Cause of Death for Patients With CV-Related Deaths in High CV Risk Pool, Trials 040 and 047

Treatment Group/ Cause of Death	Death Day	Days Since IMP	Additional Relevant Details
Bempedoic Acid			
Myocardial infarction	9	0	
	28	27	
	61	0	
	175	0	Found dead in kitchen Autopsy: consistent with acute myocardial infarction; coronary artery atheroma with probable superimposed thrombosis
	178	7	
	217	3	
	339	86	
Stroke	192	0	
Sudden death	48	30	Found unresponsive, +CPR, not resuscitated Autopsy: ischemic heart disease, hypertensive heart disease, no report of thrombosis/embolus
	114	0	Collapsed during dinner, +CPR, not resuscitated Autopsy: heart failure
	264	0	Sudden death per wife No autopsy performed
Cardiac failure	233	6	Possible pulmonary abscess and pneumonia resulting in cardiopulmonary failure
Placebo			
Cardiac arrest	170	0	Out-of-hospital cardiac arrest, temporarily resuscitated Angiogram: CAD, no thrombosis/embolus ECG: no arrythmia No autopsy performed
Sudden death	291	1	Collapsed, +CPR, not resuscitated No autopsy
Cardiopulmonary failure	54	36	"Severe cardiopulmonary failure event", no additional details provided
Unknown, +CV adjudicated	73	50	
	160	0	Died at home, no autopsy

Source: death narratives
Abbreviations: CAD, coronary artery disease; CPR, cardiopulmonary resuscitation; CV, cardiovascular, ECG, electrocardiogram; IMP, investigational medicinal product

Table 36. Cause of Death for Patients With CV-Related Deaths in Open-Label Extension Trial 050, Bempedoic Acid Treatment Group

Cause of Death	Death Day in Trial 050	Cumulative Death Day[1]	Days Since IMP	Additional Relevant Details
Myocardial infarction	205	567	1	
Myocardial ischemia (s/p CABG)	205	569	0	
Sudden death	59	407	1	No autopsy
Unknown, +CV adjudicated	337	709	0	

Source: death narratives
[1] Trial 050 is a rollover trial from Trial 040. All patients are assigned to bempedoic acid. Death days are presented based on days of exposure for bempedoic acid in Trial 050 and cumulative days of exposure from Trial 040 + Trial 050.
Abbreviations: CABG, coronary artery bypass graft; CV, cardiovascular; IMP, investigational medicinal product; s/p, status/post

Table 37. MACE and Other Serious Cardiac Events, High CV Risk Safety Population

	Trial 040[1]		Trial 047[2]		Pooled[2]		
Serious Cardiac Event	Bempedoic Acid, N=1487 n (%)	Placebo, N=742 n (%)	Bempedoic Acid, N=522 n (%)	Placebo, N=257 n (%)	Bempedoic Acid, N=2009 n (%)	Placebo, N=999 n (%)	Risk Difference (95% CI)
5-point MACE	77 (5.2)	45 (6.1)	40 (7.7)	30 (11.7)	117 (5.8)	75 (7.5)	-1.7 (-3.6, 0.2)
CV death	8 (0.5)	2 (0.3)	4 (0.8)	3 (1.2)	12 (0.6)	5 (0.5)	0.1 (-0.5, 0.6)
Nonfatal MI	14 (0.9)	11 (1.5)	2 (0.4)	2 (0.8)	16 (0.8)	13 (1.3)	-0.5 (-1.3, 0.3)
Nonfatal stroke	7 (0.5)	3 (0.4)	4 (0.8)	3 (1.2)	11 (0.5)	6 (0.6)	-0.1 (-0.6, 0.5)
Hospitalization for unstable angina	21 (1.4)	14 (1.9)	8 (1.5)	6 (2.3)	29 (1.4)	20 (2.0)	-0.6 (-1.6, 0.5)
Coronary revascularization	27 (1.8)	15 (2.0)	22 (4.2)	16 (6.2)	49 (2.4)	31 (3.1)	-0.7 (-1.9, 0.6)
3-point MACE	29 (2.0)	16 (2.2)	10 (1.9)	8 (3.1)	39 (1.9)	24 (2.4)	-0.5 (-1.6, 0.7)
Non-CV death	9 (0.6)	3 (0.4)	4 (0.8)	0 (0.0)	13 (0.6)	3 (0.3)	0.3 (-0.1, 0.8)
Hospitalization for heart failure	7 (0.5)	3 (0.4)	6 (1.1)	3 (1.2)	13 (0.6)	6 (0.6)	0.0 (-0.5, 0.6)
Non-coronary revascularization	7 (0.5)	4 (0.5)	7 (1.3)	5 (1.9)	14 (0.7)	9 (0.9)	-0.2 (-0.9, 0.5)

Source: adae.xpt; Software: JMP
[1] Based on CEC adjudication
[2] From review of MedDRA preferred terms (no CEC adjudication data available)
Abbreviations: CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; N, number of subjects in group; n, number of subjects with adverse event

Table 38. Custom MedDRA Queries,[1] High CV Risk Safety Population

	Trial 040		Trial 047		Pooled[2]		
FDA MedDRA Query[3]	Bempedoic Acid, N=1487 n (%)	Placebo, N=742 n (%)	Bempedoic Acid, N=522 n (%)	Placebo, N=257 n (%)	Bempedoic Acid, N=2009 n (%)	Placebo, N=999 n (%)	Risk Difference (95% CI)
ASCVD CMQ							
Angina	36 (2.4)	27 (3.6)	17 (3.3)	3 (1.2)	53 (2.6)	30 (3.0)	-0.4 (-1.6, 0.9)
Acute coronary syndrome	45 (3.0)	25 (3.4)	16 (3.1)	17 (6.6)	61 (3.0)	42 (4.2)	-1.2 (-2.6, 0.3)
Myocardial infarction	19 (1.3)	11 (1.5)	6 (1.1)	5 (1.9)	25 (1.2)	16 (1.6)	-0.4 (-1.3, 0.6)
Coronary artery disease	20 (1.3)	11 (1.5)	16 (3.1)	10 (3.9)	36 (1.8)	21 (2.1)	-0.3 (-1.4, 0.8)
Peripheral artery disease	18 (1.2)	12 (1.6)	6 (1.1)	5 (1.9)	24 (1.2)	17 (1.7)	-0.5 (-1.4, 0.4)
Aortic atherosclerotic disease	6 (0.4)	5 (0.7)	2 (0.4)	1 (0.4)	8 (0.4)	6 (0.6)	-0.2 (-0.8, 0.4)
Carotid artery disease	9 (0.6)	6 (0.8)	5 (1.0)	1 (0.4)	14 (0.7)	7 (0.7)	0.0 (-0.6, 0.6)
Stroke	15 (1.0)	5 (0.7)	4 (0.8)	2 (0.8)	19 (0.9)	7 (0.7)	0.2 (-0.4, 0.9)

Source: adae; Software: JMP
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CMQ, customized MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

Subset of CV Deaths Due to Other CV Events

No additional evidence supports increased risk for non-MI CV death. Sudden death and deaths from heart failure occurred with similar incidence in bempedoic acid and placebo arms (Table 35). Overall, safety analyses revealed no imbalance in heart failure or arrythmia adverse events (Table 39). Apparent imbalances in atrial and supraventricular arrhythmias occurred in some individual trials but not in others. In Trial 047, there was an imbalance in atrial fibrillation (2.1% versus 1.2%), and in Trial 040, there was an imbalance in supraventricular tachycardia (0.1% versus 0.0%). Atrial fibrillation and supraventricular imbalances were not observed in the other three trials. There were no imbalances in any other arrhythmias in any of the four clinical trials. Additionally, no changes to ECGs were observed during the trials, as presented in the Appendix (Sections 17.1.2 and 17.1.3).

There were also no changes in blood pressure or heart rate over time, as presented in the Appendix (Section 17.1.2). A CVOT is ongoing.

Table 39. Custom MedDRA Queries,[1] High CV Risk Safety Population

	Trial 040		Trial 047		Pooled[2]		
FDA MedDRA Query[3]	Bempedoic Acid, N=1487 n (%)	Placebo, N=742 n (%)	Bempedoic Acid, N=522 n (%)	Placebo, N=257 n (%)	Bempedoic Acid, N=2009 n (%)	Placebo, N=999 n (%)	Risk Difference (95% CI)
Heart Failure CMQs							
Edema	32 (2.2)	26 (3.5)	6 (1.1)	5 (1.9)	38 (1.9)	31 (3.1)	-1.2 (-2.4, 0.0)
Acute heart failure	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.4)	2 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)
Heart failure	61 (4.1)	42 (5.7)	19 (3.6)	11 (4.3)	80 (4.0)	53 (5.3)	-1.3 (-3.0, 0.3)
Cardiopulmonary failure	2 (0.1)	1 (0.1)	2 (0.4)	2 (0.8)	4 (0.2)	3 (0.3)	-0.1 (-0.5, 0.3)
Volume overload	1 (0.1)	1 (0.1)	2 (0.4)	1 (0.4)	3 (0.1)	2 (0.2)	-0.1 (-0.4, 0.3)
Hypertension	62 (4.2)	37 (5.0)	17 (3.3)	8 (3.1)	79 (3.9)	45 (4.5)	-0.6 (-2.1, 1.0)
Arrhythmia CMQs							
Atrial arrythmias	25 (1.7)	11 (1.5)	11 (2.1)	2 (0.8)	36 (1.8)	13 (1.3)	0.5 (-0.4, 1.4)
Supraventricular arrhythmias	4 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)	6 (0.3)	1 (0.1)	0.2 (-0.1, 0.5)
Bradycardia	12 (0.8)	6 (0.8)	3 (0.6)	1 (0.4)	15 (0.7)	7 (0.7)	0.0 (-0.6, 0.7)
AV block	1 (0.1)	3 (0.4)	1 (0.2)	1 (0.4)	2 (0.1)	4 (0.4)	-0.3 (-0.7, 0.1)
Tachycardia	7 (0.5)	1 (0.1)	0 (0.0)	3 (1.2)	7 (0.3)	4 (0.4)	-0.1 (-0.5, 0.4)

Source: adae.xpt; Software: JMP
[1] Treatment-emergent adverse event defined as any adverse event that occurred after the first dose of drug
[2] Pooled phase 3 population or ISS
[3] Coded as MedDRA preferred terms
Abbreviations: AV, atrioventricular; CI, confidence interval; CMQ, customized MedDRA Query; CV, cardiovascular; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

7.7.1.3. Malignancy Death Imbalance

Malignancy Deaths

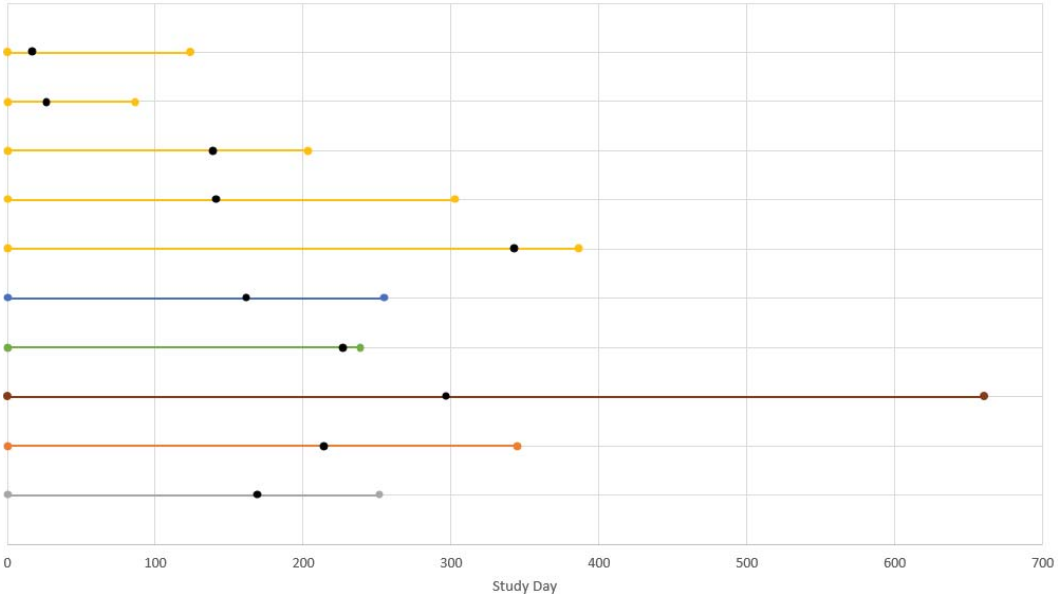
9 malignancy deaths observed in bempedoic acid-treated patients (2 expected based on 2:1 randomization)

- Malignancy deaths, 9 versus 1
  - Trial 040, 8 versus 1
  - Trial 047, 1 versus 0

Detailed reviews of death narratives and analyses of adverse events were performed to evaluate the potential for increased malignancy risk with bempedoic acid exposure. No evidence of increased malignancy-associated death risk exists when diagnoses that occurred within 6 months of treatment initiation and with fewer than 30 days of drug exposure were excluded to account for cancer latency and plausible causality. Additionally, there was no imbalance in overall malignancy diagnoses between treatment arms during the course of the trials (Table 40). Finally, there was no evidence that a particular organ or tissue type was impacted, to suggest a particular mechanism of action.

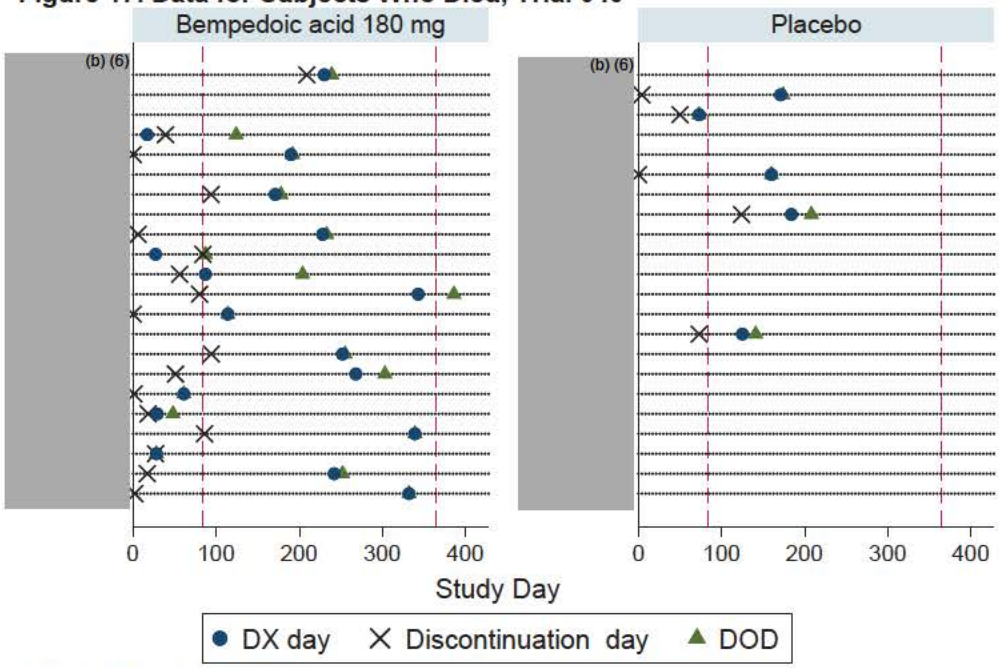
Causes of cancer death amongst bempedoic acid–exposed patients were lung (n=5), colorectal (n=1), pancreatic (n=1), renal cell (n=1), and liver metastases from an unknown primary (n=1). Amongst the five patients with lung cancer deaths, two cancer diagnoses occurred within 30 days of randomization, and two additional diagnoses occurred within 6 months of randomization. In some analyses, we excluded these diagnoses to account for cancer latency (onset prior to drug exposure) (Figure 16). Additionally, many patients diagnosed with cancer discontinued study drug within 30 days (Figure 17 and Figure 18). Minimal exposure in these patients is inconsistent with a causal association between drug exposure and cancer. Narrative review revealed that two patients (colorectal and renal cell carcinomas) died from postoperative surgical complications.

Figure 16. Malignancy Diagnosis Date



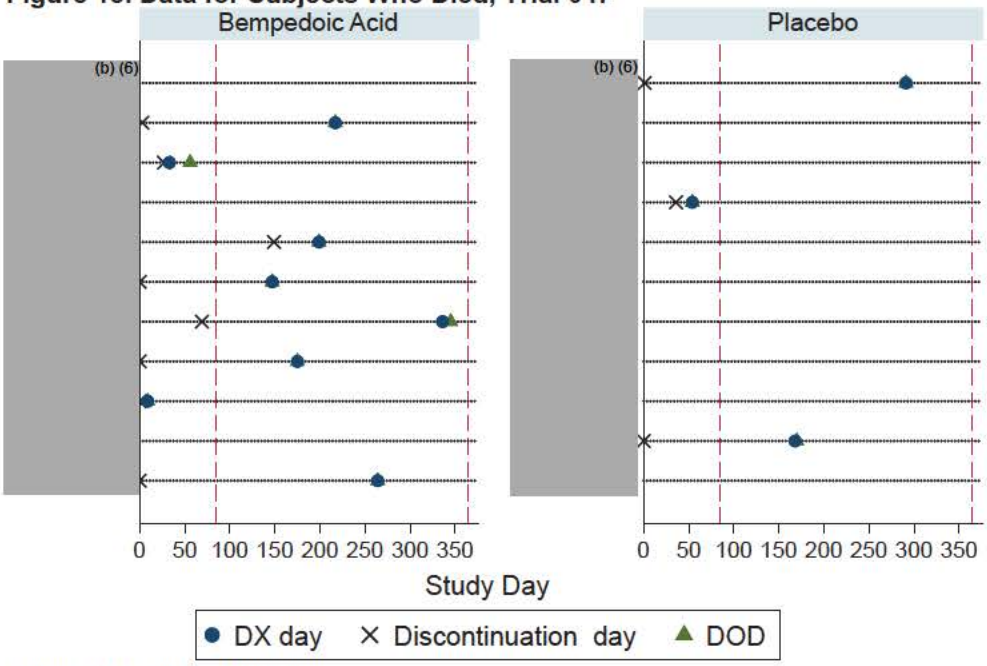
Date of diagnosis (black dot), date of death (final dot)
Lines, in order, represent: Lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, lung cancer, lung cancer, colorectal adenocarcinoma, pancreatic adenocarcinoma, gastric adenocarcinoma, renal cancer, unknown primary

Figure 17. Data for Subjects Who Died, Trial 040



Source: FDA Statistical Reviewer
Legend: Dot plot of intercurrent events. The subject id is denoted on the y axis and the day of the study is denoted on x axis. The time of study discontinuation is denoted by the cross. The time of diagnosis is depicted by blue circle and the time of death in depicted by green triangle.
Abbreviations: DX, diagnosis; DOD, day of death

Figure 18. Data for Subjects Who Died, Trial 047



Source: FDA Statistical Reviewer
Legend: Dot plot of intercurrent events. The subject id is denoted on the y axis and the day of the study is denoted on x axis. The time of study discontinuation is denoted by the cross. The time of diagnosis is depicted by blue circle and the time of death in depicted by green triangle.
Abbreviations: DX, diagnosis, DOD, day of death

Table 40. Custom MedDRA Queries,[1] High CV Risk Safety Population

	Trial 040		Trial 047		Pooled[2]		
FDA MedDRA Query[3]	Bempedoic Acid, N=1487 n (%)	Placebo, N=742 n (%)	Bempedoic Acid, N=522 n (%)	Placebo, N=257 n (%)	Bempedoic Acid, N=2009 n (%)	Placebo, N=999 n (%)	Risk Difference (95% CI)
Non-hematological malignant tumors	30 (2.0)	10 (1.3)	5 (1.0)	6 (2.3)	35 (1.7)	16 (1.6)	0.1 (-0.8, 1.1)
Adenocarcinoma of colon	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0.1 (0.0, 0.2)
Basal cell carcinoma	8 (0.5)	4 (0.5)	1 (0.2)	1 (0.4)	9 (0.4)	5 (0.5)	-0.1 (-0.6, 0.5)
Bladder cancer	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)	-0.1 (-0.3, 0.2)
Bowen's disease	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.4)	2 (0.1)	1 (0.1)	0.0 (-0.2, 0.2)
Breast cancer	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	1 (0.0)	1 (0.1)	-0.1 (-0.3, 0.2)
Gallbladder cancer	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Lip squamous cell carcinoma	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Lung adenocarcinoma	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Lung neoplasm malignant	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	0 (0.0)	0.1 (0.0, 0.3)
Lung squamous cell carcinoma metastatic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Malignant melanoma	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.0)	1 (0.1)	-0.1 (-0.3, 0.2)
Metastases to liver	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Neuroendocrine tumor of lung	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Oropharyngeal cancer	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Prostate cancer	4 (0.3)	2 (0.3)	0 (0.0)	0 (0.0)	4 (0.2)	2 (0.2)	0.0 (-0.3, 0.3)
Renal cancer	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Squamous cell carcinoma	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.4)	2 (0.1)	2 (0.2)	-0.1 (-0.4, 0.2)
Squamous cell carcinoma of skin	2 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)	3 (0.1)	1 (0.1)	0.0 (-0.2, 0.3)
Non-small cell lung cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)	-0.1 (-0.3, 0.1)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	-0.1 (-0.3, 0.1)
Ureteric cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	-0.1 (-0.3, 0.1)

FDA MedDRA Query[3]	Trial 040 Bempedoic Acid, N=1487 n (%)	Trial 040 Placebo, N=742 n (%)	Trial 047 Bempedoic Acid, N=522 n (%)	Trial 047 Placebo, N=257 n (%)	Pooled[2] Bempedoic Acid, N=2009 n (%)	Pooled[2] Placebo, N=999 n (%)	Pooled[2] Risk Difference (95% CI)
Non-hematological tumors of unspecified malignancy	6 (0.4)	1 (0.1)	2 (0.4)	1 (0.4)	8 (0.4)	2 (0.2)	0.2 (-0.2, 0.6)
Adrenal neoplasm	2 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.1)	0 (0.0)	0.1 (0.0, 0.3)
Bladder neoplasm	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0.1 (0.0, 0.2)
Brain neoplasm	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Ear neoplasm	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Renal neoplasm	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	0.0 (0.0, 0.1)
Breast neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)	-0.1 (-0.3, 0.1)
Colon neoplasm	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	-0.1 (-0.3, 0.1)
Hematological malignant tumors	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)	0.1 (0.0, 0.2)

Source: Reviewer's analysis
[1] Treatment-emergent adverse event defined as any adverse event that occurred after the first dose of drug
[2] Pooled phase 3 population or ISS
[3] Coded as MedDRA preferred terms
Abbreviations: CI, confidence interval; CV, cardiovascular; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

Malignancy is not presented for the no/low statin pool given the short trial duration of 12 to 24 weeks and small numbers of cancer diagnosed in these trials.

Table 41. Custom MedDRA Queries,[1] OLE Trial 050

FDA MedDRA Query[3]	Bempedoic Acid, N=1462 n (%)
Nonhematological malignant tumors	23 (1.6)
Basal cell carcinoma	7 (0.5)
Squamous cell carcinoma of skin	2 (0.1)
Bladder cancer	2 (0.1)
Malignant melanoma	2 (0.1)
Adenocarcinoma of colon	2 (0.1)
Colorectal cancer	1 (0.1)
Bladder transitional cell carcinoma	1 (0.1)
Prostate cancer	1 (0.1)
Renal cancer	1 (0.1)
Non–small cell lung cancer	1 (0.1)
Pancreatic carcinoma	1 (0.1)
Fibrosarcoma	1 (0.1)
Metastases to liver	1 (0.1)
Metastases to lung	1 (0.1)
Metastatic gastric cancer	1 (0.1)
Nonhematological tumors of unspecified malignancy	2 (0.1)
Adrenal neoplasm	1 (0.1)
Lung neoplasm	1 (0.1)
Hematological malignant tumors	2 (0.1)
B-cell lymphoma	1 (0.1)
Extranodal marginal zone B-cell lymphoma	1 (0.1)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; OLE, open-label extension; N, number of subjects in group; number of subjects with adverse event

7.7.2. Tendon Rupture

Issue

More bempedoic acid–treated patients experienced tendon rupture compared to placebo-treated patients.

Conclusion

Tendon rupture may be associated with bempedoic acid exposure but can be adequately mitigated via labeling, given the low incidence and identification of risk factors.

Assessment

The above conclusion is based on the following assessments: An imbalance in tendon rupture was observed with bempedoic acid exposure (11 versus 0 cases; 0.5% versus 0.0%). Tendon rupture most frequently involved the biceps tendon (n=5) or rotator cuff (n=5) but also occurred in the Achilles tendon (n=1). Tendon rupture occurred at a mean of 149 days (range 15 to 345) after starting bempedoic acid. Additional risk factors, such as concomitant use of fluoroquinolones, administration of intra-articular steroids, or past medical history of rotator cuff syndrome were identified in 4 of 11 cases; however, 7 of 11 cases had no predisposing risk factors. Note that bempedoic acid–associated tendon rupture in these two trials occurred with similar incidence to that reported for fluoroquinolones.

7.7.3. Increases in Uric Acid

Issue

More bempedoic acid–treated patients developed increases in uric acid compared to placebo-treated patients. Additionally, an imbalance in gout adverse events was noted for bempedoic acid compared to placebo.

Conclusion

Increases in uric acid and increased incidence of gout events are associated with bempedoic acid exposure but can be adequately mitigated via labeling, including a recommendation to monitor uric acid levels when clinically indicated.

Assessment

Detailed analyses were conducted to evaluate the potential for additional clinical consequence of uric acid elevation.

The above conclusion is based on the following assessments:

- Bempedoic acid inhibits OAT2, a transporter of uric acid
- Uric acid increases and gout imbalance were observed in all four clinical trials
- Uric acid increase was reversible upon drug discontinuation

Increases in serum uric acid (2.1% versus 0.5%) and an imbalance in gout adverse events (1.5% versus 0.4%) were associated with bempedoic acid exposure. Gout occurred in patients with and without a baseline history of gout. However, patients with prior history were at greater risk (gout history: 11.2% BA versus 1.7% P; RD 9.5% [2.7%, 16.3%]; no gout history: 1.0% BA versus 0.3% P; RD 0.7% [0.1%, 1.3%]). Uric acid increases were evident by Week 4 and persisted throughout treatment. By Week 12, the mean uric acid increase was 0.8 mg/dL. During the trials, 26.2% of bempedoic acid patients with normal baseline uric acid, compared to 9.5% in placebo, experienced one or more episodes of elevated uric acid level.

Because elevations in serum uric acid may result in gout or nephrolithiasis, additional analyses of these events were conducted. Of 41 gout events reported by bempedoic acid–exposed patients, one was serious and required hospitalization (2.4%), 46.3% were moderate, 7.3% were severe, 4.9% required drug discontinuation, and 31.7% did not recover or recovered with sequelae. In Trials 040, 047, 046, 048, and the OLE 050, no evidence of urinary excretion, crystal development, or nephrolithiasis was evident.

7.7.4. New-Onset Benign Prostatic Hyperplasia

Issue

An imbalance in BPH adverse events was noted for bempedoic acid compared to placebo.

Conclusion

The following risks are associated with bempedoic acid exposure but can be adequately mitigated via labeling.

Assessment

Additional analyses were conducted to evaluate clinical relevance. The above conclusion is based on the following assessments: Imbalances in new-onset BPH were observed in both long-term trials.

In the long-term trials (high CV risk pool), bempedoic acid was associated with an increased risk of new-onset BPH (1.3% versus 0.1%) at a mean of 6 months. No cases were reported in the short-term trials (12 to 24 weeks), possibly due to the shorter treatment duration.

Of the 20 BPH cases reported amongst bempedoic acid–treated patients, 5 (25%) cases were serious and required hospitalization, 4 (20%) cases required surgical intervention (transurethral resection of the prostate [TURP] or prostatectomy), and 15 (75%) cases did not recover or recovered with sequelae.

In Trial 047, there was an imbalance in genitourinary infections in men treated with bempedoic acid compared to placebo (4.0% versus 1.2%). However, the imbalance in Trial 040 was smaller (bempedoic acid 5.6% versus placebo 5.3%). The clinical significance of this finding is therefore uncertain. There was no other evidence to support urinary retention, such as differences in BUN/Cr between men and women.

Prostatic hypertrophy was not observed in nonclinical studies. Testosterone levels were not measured in nonclinical or clinical studies.

7.7.5. Decreased Hemoglobin

Issue

More bempedoic acid–treated patients experienced decreases in hemoglobin than placebo-treated patients.

Conclusion

Bempedoic acid is associated with hemoglobin decline in nonclinical and clinical studies. However, our analyses suggest that hemoglobin decreases were not associated with any adverse clinical sequelae. The observed decreases in hemoglobin associated with bempedoic acid can be communicated in labeling.

Assessment

Additional analyses were performed to evaluate the clinical meaningfulness of hemoglobin decrease. The above conclusion is based on the following assessments:

- Hemoglobin decrease was observed in nonclinical animal studies
- Hemoglobin decrease was observed in all four clinical trials
- Hemoglobin decrease was reversible upon drug discontinuation

Evidence of hemoglobin decline was observed throughout the trial, beginning at Week 4. For most patients, the mean change in hemoglobin was minimal, -0.26 to -0.59 g/dL from baseline to Week 52. However, 3.4% to 8.0% of bempedoic acid–treated patients had hemoglobin decline ≥2 g/dL from baseline (compared to 0.0% to 3.7% placebo), and 1.4% to 1.7% had decline ≥3 g/dL (compared to 0.0% to 1.3% placebo).

Amongst patients who experienced ≥2-point decline, there were no identifiable risk factors or alternative explanation in the majority (94%) of cases. However, in general, there were no apparent clinical manifestations (such as need for transfusion). Most patient's values remained within normal limits despite the decline (amongst patients who dropped, mean Hgb BL 14.9 g/dL to mean Hgb FU 12.3 g/dL).

7.7.6. Decreased White Blood Cell Count

Issue

More bempedoic acid–treated patients experienced decreases in total WBC than placebo-treated patients.

Conclusion

Bempedoic acid is associated with minimal decline in neutrophils and total WBC. There may be evidence of clinical consequence, namely increased risk of skin or soft tissue infections. The risk of decreased WBC and neutrophils associated with bempedoic acid exposure can be adequately mitigated via labeling.

Assessment

Detailed analyses were conducted to evaluate whether decreases in WBC had a clinically meaningful consequence. The above conclusion is based on the following assessments:

- WBC decrease was observed in all four clinical trials
- In all trials, changes in WBC were due to neutrophil decline; no other components were affected

Evidence of WBC decline was observed beginning at Week 4 and maintained throughout the trial. For most patients, the mean decline was minimal, -0.1 to -0.5×10^9/L. However, 3.5 to 9.0% of bempedoic acid–treated patients, who had normal WBC at baseline, developed leukopenia at least once during the trial. There were no identifiable risk factors for patients who developed leukopenia and no strong evidence to suggest an increased risk of infection with bempedoic acid exposure. The only observable difference was a small imbalance in several skin/soft tissue

infections in the high CV risk pool: cellulitis (0.8% versus 0.4%), erysipelas (0.2% versus 0.0%), and wound infection (0.5% versus 0.3%). A small imbalance in gastroenteritis was also observed (1.7% versus 1.3%) but may be confounded by bempedoic acid–associated diarrhea. There was no evidence of imbalance in other infections such as UTI, URI, influenza, otitis media, or abscesses in any trial.

7.7.7. Changes in Renal Lab Parameters

Issue

More bempedoic acid–treated patients experienced increases in creatinine, increases in BUN, and decreases in eGFR than placebo-treated patients.

Conclusion

Analyses do not support direct renal toxicity by bempedoic acid. Changes in renal lab parameters are most likely related to concomitant OAT2 inhibition by bempedoic acid. The observed increases in BUN and creatinine associated with bempedoic acid exposure but can be adequately communicated via labeling.

Assessment

Detailed analyses were performed to evaluate the potential for renal toxicity in patients with elevated renal lab parameters. The above conclusion is based on the following assessments:

- Changes in renal lab parameters were observed in nonclinical animal studies
- Changes were observed in all four clinical trials
- Changes were reversible upon drug discontinuation
- No evidence of clinical consequence (acute kidney injury, renal failure, or proteinuria) in patients with elevated lab parameters

Overall, bempedoic acid exposure was associated with small increases in BUN/Cr (BUN: +1.9 mg/dL, Cr +0.05 mg/dL), beginning at Week 4 and sustained throughout treatment. Clinically relevant changes to BUN/Cr/eGFR, such as >30% increase from baseline or shift from normal baseline to > ULN, were frequent but did not result in any apparent clinical consequence. There was no evidence of acute kidney injury or proteinuria during the trial.

An imbalance in renal failure AEs was observed (0.9% versus 0.1%). However, in all but two cases these AEs reflected increased serum BUN (range: +6 to 18 mg/dL from BL) or creatinine (range: +0.07 to 0.8 mg/dL from BL) amongst patients with baseline history of renal insufficiency with no clinical evidence of renal failure. In these cases, BUN/Cr returned to baseline without clinical intervention or drug discontinuation. In clinical practice, these changes to renal lab parameters would most likely be monitored by physicians without requiring intervention.

In the additional two cases, neither could be directly attributed to bempedoic acid. One patient required hospitalization at Day 54 when creatinine increased from 1.3 to 6.7 mg/dL and BUN increased from 20 to 70 mg/dL. The patient was treated with IVF hydration, discontinued

bempedoic acid therapy, and was released from the hospital on Day 61. No hemodialysis was required. However, CT scan obtained during hospitalization demonstrated bilateral atrophic kidneys, which suggests a chronic etiology of renal failure and is difficult to attribute to bempedoic acid given the short duration of drug exposure. In the second case, the patient's BUN/Cr peaked at 76/2.7 mg/dL at Day 85 (baseline: 36/1.4 mg/dL). No follow-up values were provided to demonstrate resolution; however, no clinical intervention was required, and the patient remained on drug until Day 157 when discontinuation occurred poststroke.

Additionally, the patient's concomitant medication use included multiple drugs associated with increases in BUN and/or creatinine, including a diuretic, an ACE inhibitor, and various antibiotics (including ceftriaxone) in the setting of frequent hospitalizations for COPD exacerbations and stroke

7.7.8. Thrombocytosis

Issue

More bempedoic acid–treated patients experienced increases in platelets compared to placebo-treated patients.

Conclusion

The increases in platelet count are unlikely clinically meaningful. The association with increases in platelet count can be communicated in labeling.

Assessment

Detailed analyses were conducted to evaluate the potential for clinical consequence of platelet elevation. The above conclusion is based on the following assessments:

- Platelet elevation was observed in all four clinical trials
- For most patients, the degree of elevation was minimal, and values generally remained within normal limits
- No evidence of increased incidence of thromboembolic events

Minor platelet elevation was observed with bempedoic acid exposure. Although more bempedoic acid patients experienced doubling of platelet counts from baseline or increases to $>500\times10^9$/L, the incidence was <1% and platelet values for these patients generally remained at levels low enough to exclude clinical consequence. There was no imbalance in platelet increase to $>750{,}000\times10^9$/L, the level generally associated with increased thrombotic risk. Additionally, no imbalances in thromboembolic events were identified in review of TEAEs.

7.7.9. Decreased Alkaline Phosphatase

Issue

More bempedoic acid–treated patients experienced decreases in alkaline phosphatase than placebo-treated patients.

Conclusion

The decreases in alkaline phosphatase are unlikely clinically meaningful. The observed decreases in alkaline phosphatase can be communicated in labeling.

Assessment

Detailed analyses were performed to evaluate the potential for clinical consequence of platelet elevation. The above conclusion is based on the following assessments:

- Alkaline phosphatase decline was observed in all four clinical trials
- The degree of decline was minimal, and values generally remained within normal limits (decreases from baseline of 11 to 14 points)
- No evidence of bone fractures or bone disorder

7.7.10. Imbalance in Pancreatic Tumors in the Rat Carcinogenicity Study

Issue

In the 2-year oral carcinogenicity study in rats, increases in the combined incidence of pancreatic islet cell adenomas and carcinomas were observed in males treated with bempedoic acid resulting in systemic exposures that approximate the clinical exposure at the human dose of 180 mg. The Applicant concluded that the pancreatic tumor finding is human irrelevant based on the presence of the finding in only a single sex of one species and the absence of distribution and activation of bempedoic acid in the pancreases. The Applicant considered expert opinion that outlined differences in pathogenesis, classification, lesion progression, and metastatic potential of the rat pancreatic lesion as compared to comparable human lesions.

Conclusion

Labeling is proposed that describes the increased incidence in pancreatic tumors, including exposure multiples and a statement that the clinical relevance of this finding is unclear.

Assessment

The Division considered the following nonclinical data to support the inclusion of pancreatic tumor finding in the label with language describing the human relevance of the tumors as unknown:

- The combined incidences of pancreas islet cell adenoma (10.8%) and carcinoma (3.1%) were higher than the historical control range reported at the testing facility (adenoma,1.5-10%; carcinoma, 0-1.7%).
- Review by CDER's Executive Carcinogenicity Assessment Committee concluded that pancreas tumor findings in male rats were consistent with a drug-related effect and met the FDA's statistical criteria for a drug-related increase by both trend and pairwise analysis.
- Limited distribution of bempedoic acid to the pancreas was noted for rats. While ACSVL1 (bempedoic acid-activating enzyme) is not expressed in the pancreas, high expression of the pharmacological target enzyme ACL is observed in the pancreas.
- Differences in interspecies and intersex susceptibility to tumors is well established. In rodent carcinogenicity studies, higher background incidence rates are noted for some cancer types in males compared to females, which might be attributable to sex-specific cellular, molecular and/or hormonal differences (i.e., protective for females and facilitative for males). Therefore, the finding in only a single sex of rats does not, on its own, rule out human relevance.
- No data are available regarding the mechanism(s) by which bempedoic acid causes pancreatic islet cell tumors in male rats. Understanding the underlying mechanism of treatment-related pancreas islet cell tumor findings is critical to a definitive assessment of human relevance.
- ACL inhibition is a novel pharmacological target and there is insufficient prior human use data available to inform the risk.
- Long-term clinical studies and post-marketing experience might further address this nonclinical finding.
- In the absence of an established mechanism for pancreas tumor formation in male rats or long-term human exposure data, human relevance of islet cell tumors observed in male rats cannot be excluded.

7.7.11. Toxicological Interactions Between Bempedoic Acid and Statins

Issue

Synergistic toxicologic interactions occurred between bempedoic acid and atorvastatin resulting in deaths, hypoglycemia and adverse liver toxicities in monkeys at doses of potential clinical relevance, based on reduced safety margins compared to each drug administered alone.

Conclusion

Interactions between statins and bempedoic acid are not likely a significant safety concern.

Assessment

The findings below were considered to support the conclusion.

- Toxicological interactions, including hypoglycemia, liver toxicities and mortalities were evident in monkeys at doses resulting in exposures above the clinical exposure.

- Imbalances in hypoglycemia lactic acidosis, and adverse liver toxicities were not observed in bempedoic acid clinical trials. No clinical trial deaths were attributable to hypoglycemia, lactic acidosis, or liver toxicity.

In clinical trials, no imbalance in hypoglycemia events was observed between bempedoic acid and placebo (Table 42 and Table 43), and none of the death events was due to hypoglycemia or lactic acidosis. Two patients treated with bempedoic acid were reported to have experienced lactic or metabolic acidosis adverse events; however, neither appears to be drug-induced or clinically significant (see Narratives below). Carbon dioxide and chloride were monitored in Trial 040, and there were no significant changes from baseline to Week 52 (Appendix, Section 16.2.3). Blood pH was not monitored in any trial.

Narrative, lactic acidosis

A 60-year-old white female with T2DM on metformin. Diagnosed with dehydration and lactic acidosis in setting of food poisoning after seafood ingestion on Day 24. Treated with antibiotics; resolution by Day 26. Continued bempedoic acid treatment without issue. Unlikely drug-related.

Narrative, metabolic acidosis

A 61-year-old white female with reported mild metabolic acidosis on Day 267; resolved at Day 359. Diagnosis appears to be based on slight electrolyte abnormalities (uric acid 9.0 mg/dL [ULN 5.9], carbon dioxide 21 mEq/L [LLN 23], phosphorus 5.4 mg/dL [ULN 4.7]). Remainder of lab values, including chloride, BUN, creatinine, and glucose were within normal limits. No pH was collected but is likely to be abnormal based on review of electrolytes. Patient was asymptomatic.

Table 42. Hypoglycemic Events, High CV Risk Safety Population

	Trial 040[1]		Trial 047[2]		Pooled		
Hypoglycemic Event	Bempedoic Acid, N=1487 n (%)	Placebo, N=742 n (%)	Bempedoic Acid, N=522 n (%)	Placebo, N=257 n (%)	Bempedoic Acid, N=2009 n (%)	Placebo, N=999 n (%)	Risk Difference (95% CI)
Level 1 Hypoglycemia[3]	20 (1.3)	15 (2.0)	6 (1.1)	3 (1.2)	26 (1.3)	18 (1.8)	-0.5 (-1.5, 0.5)
Level 2 Hypoglycemia[4]	7 (0.5)	4 (0.5)	4 (0.8)	1 (0.4)	11 (0.5)	5 (0.5)	0.05 (-0.5, 0.6)
Level 3 Hypoglycemia[5]	1 (<0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.05)	1 (0.1)	-0.05 (-0.3, 0.2)
Hypoglycemic coma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Hypoglycemic seizure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Hypoglycemic unconsciousness	1 (<0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.05)	1 (0.1)	-0.05 (-0.3, 0.2)
Acidosis	1 (<0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)	0.1 (-0.04, 0.2)
Lactic acidosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.05)	0 (0.0)	0.05 (-0.05, 0.1)
Metabolic acidosis	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.05)	0 (0.0)	0.05 (-0.05, 0.1)
Diabetic ketoacidosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)

Source: adae.xpt, adlbchem.xpt; Software: JMP
[1] Based on CEC adjudication
[2] From review of MedDRA preferred terms (no CEC adjudication data available)
[3] Serum glucose <70 mg/dL and ≥54 mg/dL
[4] Serum glucose <54 mg/dL
[5] A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia
Abbreviations: CV, cardiovascular; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

Table 43. Hypoglycemic Events, No/Low Statin Safety Population

	Trial 046		Trial 048		Pooled		
Hypoglycemic Event	Bempedoic Acid, N=234 n (%)	Placebo, N=111 n (%)	Bempedoic Acid, N=181 n (%)	Placebo, N=87 n (%)	Bempedoic Acid, N=415 n (%)	Placebo, N=198 n (%)	Risk Difference (95% CI)
Level 1 Hypoglycemia[1]	4 (1.7)	1 (0.9)	2 (1.1)	0 (0.0)	6 (1.4)	1 (0.5)	0.9 (-0.6, 2.5)
Level 2 Hypoglycemia[2]	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	1 (0.5)	-0.3 (-1.4, 0.8)
Level 3 Hypoglycemia[3]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Hypoglycemic coma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Hypoglycemic seizure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Hypoglycemic unconsciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Acidosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Lactic acidosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Metabolic acidosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Diabetic ketoacidosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)

Source: adae.xpt, adlbchem.xpt; Software: JMP
[1] Serum glucose <70 mg/dL and ≥54 mg/dL
[2] Serum glucose <54 mg/dL
[3] A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia
Abbreviations: CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

Based on the findings from a hepatic impairment study (Study 032), both AUC_{inf} and C_{max} of bempedoic acid were similar between subjects with normal hepatic function and mild/moderate hepatic function. No dose adjustment is recommended. For detailed information, see Section 14.2.8.2.

Renal Impairment

Based on the findings from a renal impairment study (Study 023), both AUC_{inf} and C_{max} of bempedoic acid increased approximately 50% in subjects with mild renal impairment (eGFR >90 mL/min), and 130% in subjects with moderate (eGFR 60 to 89 mL/min) and severe (eGFR 30 to 59 mL/min) renal impairment. Similar renal impairment effect on bempedoic acid systemic exposure was demonstrated based on observed bempedoic acid trough concentrations at steady state.

Based on the reviewer's assessment of the data between patients with normal renal function or mild renal impairment and patients with moderate renal impairment on LDL-C lowering effect for efficacy evaluation, uric acid, eGFR, creatinine, BUN, and hemoglobin for safety evaluation, no dose adjustment in patients with moderate renal impairment is recommended. For detailed information, see reviewer's assessment of renal impairment effect on efficacy and safety in Section 14.2.8.3.

Other Factors

Based on population pharmacokinetic analysis, age, gender, race, and body weight had no clinically meaningful impact on bempedoic acid systemic exposure. No dose adjustment is necessary for these intrinsic factors. For detailed information, see Section 14.2.8.1.

8.2. Drug Interactions

Bempedoic acid, as an add-on therapy, interacted with some of its background therapy, statins. When coadministered with bempedoic acid, there was a general increase of systemic exposure for statins. As indicated in Section 8.1, the majority of the patient population had mild renal impairment and bempedoic acid exposure in this population increased by 50% in comparison to subjects with normal renal function. Therefore, the most relevant metric to be used for evaluating statin dose in population with mild renal impairment receiving a 180 mg bempedoic acid dose should be the drug-drug interaction (DDI) evaluation in healthy volunteers with 240 mg QD bempedoic acid (as 270 mg dose was never evaluated). A brief summary of the relevant DDI evaluation are shown in Table 44 and Table 45 below.

Table 44. Relevant DDI Study Results in Healthy Volunteers, 240 mg Bempedoic Acid, Once Daily

Statin	AUC	C_{max}
Atorvastatin (10 mg)[1]	1.77	1.69
Atorvastatin ortho-hydroxy	1.76	1.81
Simvastatin (20 mg)	1.29	0.99
Simvastatin acid	1.91	1.43
Pravastatin (40 mg)	1.99	2.04
Rosuvastatin (10 mg)	1.69	2.08

Source: Table 11, Table 12, Table 14, and Table 16 in Study 012 CSR
[1] Evaluated in subjects with hypercholesterolemia
Abbreviations: DDI, drug-drug interaction

Table 45. Relevant DDI Study Results in Patients With Hyperlipidemia, 180 mg Bempedoic Acid, Once Daily

Statin	AUC	C_{max}
Atorvastatin (80 mg)	1.29	0.99
Atorvastatin ortho-hydroxy	1.22	1.03

Source: Table 11-4 and Table 11-5 in Study 035 CSR
Abbreviations: DDI, drug-drug interaction

Simvastatin

During the phase 2 drug development, a case of rhabdomyolysis in a patient with eGFR of 55 mL/min on bempedoic acid+simvastatin 40 mg was reported.

The risk of myopathy, including rhabdomyolysis, is simvastatin dose related. In a clinical trial database in which 41,413 patients were treated with ZOCOR, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03% and 0.08% at 20 and 40 mg/day, respectively. The incidence of myopathy with 80 mg (0.61%) was disproportionately higher than that observed at the lower doses.

Due to the increased risk of myopathy, including rhabdomyolysis associated with the 80-mg dose of ZOCOR, patients unable to achieve their LDL-C goal utilizing the 40-mg dose of ZOCOR should not be titrated to the 80-mg dose but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering. (Source: ZOCOR (simvastatin) tablets package insert, section 5.1 Myopathy/Rhabdomyolysis and section 2.2 Restricted Dosing for 80 mg.[1]

Considering the 100% increase in simvastatin acid systemic exposure when coadministered with 240 mg bempedoic acid, and the current dosing recommendation for simvastatin, the following procedures should be taken when co-administering bempedoic acid with simvastatin:

Avoid concomitant use of bempedoic acid with simvastatin greater than 20 mg.

(See detailed information in Section 14.2.7.)

[1] Accessed November 7, 2019, at https://www.accessdata fda.gov/drugsatfda_docs/label/2019/019766s100lbl.pdf

Pravastatin

Bempedoic acid (240 mg) increased pravastatin systemic exposure by 100% in healthy volunteers. The following procedures should be taken when co-administering bempedoic acid with pravastatin:

Avoid concomitant use of bempedoic acid with pravastatin greater than 40 mg.

(See detailed information in Section 14.2.7.)

Atorvastatin

In Study 012, 10 mg QD atorvastatin was coadministered with 240 mg QD bempedoic acid in healthy volunteers. The systemic exposure of atorvastatin and atorvastatin ortho-hydroxy were increased 76% and 76%, respectively. In addition, one DDI study (Study 037) with atorvastatin 80 mg QD was conducted in patients with hyperlipidemia. When bempedoic acid 180 mg QD was coadministered with atorvastatin 80 mg QD, only 20% to 30% systemic exposure of atorvastatin was observed. Therefore, no dose adjustment for atorvastatin is recommended. (See detailed information in Section 14.2.7.)

Rosuvastatin

In Study 012, 10 mg QD rosuvastatin was coadministered with 240 mg QD bempedoic acid in healthy volunteers. The systemic exposure of rosuvastatin increased by 69%. Therefore, no dose adjustment is recommended. (See detailed information in Section 14.2.7.)

Other DDI Studies

DDI studies were also conducted with an oral contraceptive (Ortho-Novum 1/35), UGT inhibitor probenecid, metformin, and ezetimibe, in healthy volunteers. Based on the DDI findings, no dose adjustment for oral contraceptive, probenecid, metformin, and ezetimibe is recommended. (See detailed information in Section 14.2.7.)

8.3. Plans for Pediatric Drug Development

As a new active ingredient, this application is subject to Pediatric Research Equity Act requirements. Under the iPSP agreed to by the Division and Applicant, the Applicant was granted a partial waiver for pediatric patients with HeFH less than 10 years of age as studies are impossible or highly impractical. The Applicant will be issued postmarketing requirements (PMRs) to conduct a phase 2 pharmacokinetic/pharmacodynamic study and a phase 3 efficacy and safety study evaluating bempedoic acid in patients with HeFH ages 10 years to less than 18 years.

8.4. Pregnancy and Lactation

Animal Data

Nonclinical reproduction studies covering the entire cycle of reproduction in rats, and the period of organogenesis in rabbits, were conducted to inform potential risks to humans during pregnancy and lactation, as well as the potential to affect fertility. The following section describes the outcomes and conclusions of these studies. Greater details of the reproductive toxicity studies are provided in the Section 13 and the final recommended labeling is shown in Section 21.

Table 46. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	Embryo-fetal developmental toxicity study in rats showed increases in the incidence of nonadverse fetal skeletal variations (bent long bones, bent scapula and incomplete ossification) at doses ≥10 mg/kg/day (below the clinical exposure at human dose of 180 mg, based on AUC). Adverse effect on uterine parameters (decreases in the numbers of viable fetuses, increases in postimplantation loss and increased total resorptions) at 60 mg/kg/day (11 times the clinical exposure at the human dose of 180 mg based on AUC) and lowered fetal body weight were observed at ≥30 mg/kg/day (4 times the clinical exposure at the human dose of 180 mg, based on AUC). Maternal toxicities in the form of reduced body weight and food consumption were noted at ≥30 mg/kg/day (day (4 times the clinical exposure at the human dose of 180 mg, based on AUC). Bempedoic acid caused no adverse developmental outcomes in pregnant rabbits at doses up to 80 mg/kg/day (12 times the clinical exposure at the human dose of 180 mg, based on AUC). In a rat pre- and postnatal development study, treatment with bempedoic acid was associated with adverse delivery outcomes, including increases in stillborn pup and reductions in numbers of live pups, pup survival, pup growth, and slight delays in learning and memory at ≥10 mg/kg/day (below the clinical exposure at human dose of 180 mg, based on AUC). However, doses ≥10 mg/kg/day were associated with maternal toxicities.
8.2 Lactation	The partitioning of bempedoic acid into animal milk is not studied.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	In a rat fertility study, no adverse effect on male fertility was observed even though there were drug-related decreases in sperm count that occurred at 60 mg/kg/day (9 times the clinical exposure at the human dose of 180 mg, based on AUC). In females, there were decreases in the numbers of corpora lutea, implants, viable embryos and litter size at ≥30 mg/kg/day (4 times the clinical exposure at the human dose of 180 mg, based on AUC) and changes in estrus cyclicity were observed in females treated at 60 mg/kg/day (9 times the clinical exposure at the human dose of 180 mg, based on AUC). General toxicity was noted in both males and females at ≥30 mg/kg/day.

The low safety margins identified from fertility, embryo-fetal and pre-and postnatal development studies conducted in rat (Table 47) are considered acceptable, because the adverse effects were only observed at maternally toxic doses. Additionally, the adverse effects observed in offspring were consistent with the type and degree of maternal toxicity observed. Hence, these effects are considered unlikely to be clinically relevant.

Table 47. Bempedoic Acid Reproductive Toxicity Safety Margins

Study	NOAEL (mg/kg)	Nonclinical Exposure[1] (µg.h/mL)	Safety Margins[2] (multiples)	Basis for NOAEL
Fertility rat	10 mg/kg/day	58.5[3]	<1	Adverse female reproductive indices (increases in early embryonic deaths, lower corpora lutea, implants and litter sizes) at ≥30 mg/kg/day.
EFD rat	30 mg/kg/day	1418	4	Lower fetus viability, postimplantation loss, increased postimplantation loss, increased resorption and reduced litter size at 60 mg/kg/day.
EFD rabbit	80 mg/kg/day	3906	11	No adverse effect on embryo-fetal development at the highest dose (80 mg/kg/day) tested.
PPND rat	5 mg/kg/day	89.7[4]	<1	Adverse effects on delivery including, increases in stillborn pup, reductions in numbers of live pups, pup survival, pup growth and slight delays in learning and memory at doses ≥10 mg/kg/day.

Source: Nonclinical Reviewer
[1] Exposure is the sum of ETC-1002 and ESP12588
[2] Safety margins were based on population pharmacokinetics analysis from phase 3 trials, where the maximum clinical dose resulted in systemic geometric mean combined ETC-1002 and ESP15228 exposures (AUC_{0-24hr}) of 340 µg.hr/mL
[3] No PK data; based on 6-month study (Day 180)
[4] No PK data: extrapolated from GD17 exposure rat EFD study assuming linear proportionality
Abbreviations: EFD, embryo-fetal development; NOAEL, no observed adverse effect level; PPND, pre- and postnatal

Human Data

The Division of Pediatric and Maternal Health (DPMH) completed a consult review regarding proposed labeling to comply with the Pregnancy and Lactation labeling rule. The following summarizes DPMH's conclusions.

Pregnancy

There are minimal human pregnancy data (and no outcome data) for bempedoic acid in the published literature and in the Applicant's PVDB. The findings in animal studies with minor skeletal variations at doses below the clinical exposure were not worrisome. The Applicant recommended a (b) (4) regarding the use in pregnancy based on the animal studies and mechanism of action. DPMH recommends removing the (b) (4) and replacing it with a notice of the possibility of fetal harm based on mechanism of action in Section 8.

Because there are insufficient human data available to inform the safety of bempedoic acid use during pregnancy from clinical trial experience and the Applicant's pharmacovigilance database, DPMH recommends a PMR for a pregnancy exposure registry and a postmarketing pregnancy study of a different design to assess the safety of bempedoic acid during pregnancy.

Lactation

Based on the high protein binding (99%), it is unlikely that significant amounts of bempedoic acid would be present in human milk. However, because of theoretical concerns, DPMH proposes a PMR for a milk-only lactation study to confirm a low level being present in human milk. Should a significant amount of bempedoic acid be found in the milk-only lactation study, a milk-plasma study should be considered.

DPMH proposes the following for the "Risk Summary" labeling in Section 8.2:

(b) (4)

(b) (4)

9. Product Quality

Approval.

The Office of Pharmaceutical Quality Review team assessed NDA 211616 with respect to Chemistry, Manufacturing, and Controls (CMC) and determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective.

Nexletol (bempedoic acid) tablet is an immediate-release dosage and contains 180 mg of bempedoic acid. Bempedoic acid is a new chemical entity. Nexletol tablets are white to off-white oval shaped film-coated tablets debossed with "ESP" on one side and with (b) (4) on the other side. Nexletol tablets are packaged in 30 ct or 90 ct HDPE bottle supplied with desiccant or as provided as 7 ct PVC blister pack samples. Nexletol should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

9.1. Device or Combination Product Considerations

N/A

10. Human Subjects Protections / Clinical Site and Other GCP Inspections / Financial Disclosure

The inspection for this NDA covering three clinical trials consisted of five domestic and three foreign clinical sites representing 10 study sites, in addition to the Applicant.

The inspection of two clinical investigators and the Applicant revealed regulatory deficiencies which are unlikely to have a significant impact on overall results. The inspection of the remaining clinical investigators revealed no regulatory violations. Based on the inspections, the study data generated are considered acceptable and may be used in support of this NDA.

For more information, see Section 20.

11. Advisory Committee Summary

N/A

III. Appendices

12. Summary of Regulatory History

IND 106654 was submitted September 23, 2009, to study ETC-1002 (later called bempedoic acid) for the treatment of dyslipidemia. Initial agency reviews described the compound as a dual peroxisome proliferator activated receptor (PPAR) (α, γ) agonist. As with all PPAR agonists submitted to the Division since around 2004, the IND was put on Partial Clinical Hold on November 19, 2009, for clinical studies in excess of 6 months until draft reports from completed 2-year rat and mouse carcinogenicity studies were submitted. Special Protocol Assessment requests were submitted for the proposed rat and mouse carcinogenicity studies on February 10, 2012, and March 20, 2012, respectively; agreement letters issued March 29, 2012, and May 3, 2012, respectively. Following submission of completed carcinogenicity study reports, that Partial Clinical Hold was removed January 29, 2015.

Bempedoic acid was later determined to be an ACL inhibitor. According to the firm, ACL is an enzyme upstream of HMG-CoA reductase (target for statins) in the cholesterol biosynthesis pathway. Inhibition of ACL by ETC-1002-CoA results in decreased cholesterol synthesis in the liver and subsequent upregulation in LDL receptors on the surface of the liver, ultimately leading to increased LDL-C clearance from the blood.

Due to inhibition of the statin pathway and lack of cholesterol synthesis inhibition in the skeletal muscle, the firm anticipated similar efficacy and a better adverse event profile than statins.

On December 12, 2012, the application was placed on partial clinical hold for daily doses in excess of 240 mg based on unexplained deaths in rats and monkeys. The partial clinical hold was removed July 1, 2015, once the cause of death was identified and appropriate clinical monitoring was proposed, but the Applicant notified FDA of their intent to limit daily dosing to 180 mg.

In response to a May 7, 2015, meeting request, an EOP2 meeting was held on August 11, 2015, to discuss the firm's development plan for the following proposed indications: ETC-1002 is indicated as an adjunctive therapy to diet (b) (4)

(b) (4)

In the August 5, 2015, preliminary comments for the EOP2 meeting, the Division expressed reservations that the Applicant appeared to be (b) (4)

(b) (4)

(b) (4)

The day prior to the scheduled August 11, 2015, meeting, the firm submitted a revised clinical study plan, which included a revised proposed indication: "ETC 1002 is indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or (b) (4) atherosclerotic cardiovascular disease (ASCVD) (b) (4) additional lowering of LDL C." Meeting minutes issued on September 10, 2015.

Following the EOP2 meeting, on November 9, 2015, Esperion requested (b) (4)

(b) (4)

On January 26, 2016, the firm submitted protocol 1002-043, titled, *A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effects of Bempedoic Acid (ETC 1002) on the Occurrence of Major Cardiovascular Events in Patients with, or at high risk for, Cardiovascular Disease who are Statin Intolerant* for review under the Special Protocol Assessment process. A "No Agreement" letter issued on March 11, 2016. The firm resubmitted a revised protocol on April 21, 2016, and a "No Agreement" letter issued June 8, 2016. Despite nonagreement on the Special Protocol Assessment, at a Type A Meeting held February 7, 2017, the Division ultimately agreed to a compromise definition of statin intolerance, coupled with additional informed consent provisions, for the purposes of conducting the CVOT. That study is currently ongoing, and the plan is (b) (4)

On February 5, 2016, the firm submitted Study 1002-022 titled *A Randomized, Double-Blind, Placebo- and Positive-Controlled, Parallel Design Study to Evaluate the Effect of ETC-1002 on the QT/QTc Interval in Healthy Volunteers*. On April 14, 2016, the Applicant was notified that no significant QTc prolongation effect was detected in this thorough QT/QTc study.

On February 18, 2016, the firm requested a meeting to obtain the Agency's advice and agreement on the newly proposed phase 3 clinical development program and discussion of a

(b) (4)

An Initial Agreement letter issued May 4, 2016 for their proposed pediatric study plan which was submitted for the following indications:

1. Bempedoic acid is indicated as an adjunct to diet and maximally tolerated statins for treatment of adults with HeFH or with ASCVD who require additional lowering of LDL-C.

(b) (4)

In a submission dated March 1, 2017, the firm requested (b) (4)

A pre-NDA CMC meeting was requested May 21, 2018, granted May 31, 2018, and written responses issued August 1, 2018.

A pre-NDA clinical/pharmacology/toxicology meeting was requested May 25, 2019, granted May 31, 2019, and preliminary responses were issued August 28, 2018. The Applicant found these responses acceptable and the meeting scheduled for September 6, 2018, was cancelled.

The Applicant's initial proposed trade name, (b) (4), was found unacceptable on July 3, 2017. A subsequently proposed trade name, Nexletol, was found conditionally acceptable on January 2, 2018.

The May 25, 2018, pre-NDA meeting request includes the following proposed indication for the initial submission:

"Bempedoic acid is indicated as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with Heterozygous Familial Hypercholesterolemia (HeFH) or Atherosclerotic Cardiovascular Disease (ASCVD) who require additional LDL-C lowering."

According to the meeting package submitted June 29, 2018, the firm has again revised the proposed indication as follows:

(b) (4)

This is the indication that was proposed when the NDA was submitted on February 20, 2019.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under IND

13.1.1. Pharmacology

13.1.1.1. Primary Pharmacology

Bempedoic acid (ETC-1002) is a prodrug that is converted to ETC-1002-coenzyme A (ETC-1002-CoA) in the liver and inhibits human ACL (K_i =2μM), an enzyme that generates cytosolic acetyl-CoA from citrate used as substrate for the de novo synthesis of cholesterol and fatty acids. By reducing hepatic cholesterol biosynthesis, bempedoic acid causes upregulation of hepatic LDLRs that enhances LDL-C clearance by the liver in a manner similar to statins.

In Vitro Activity Supporting Mechanism of Action

- Consistent with the proposed mechanism of action, ACL inhibition, mechanistic studies in primary rat hepatocytes showed that treatment with bempedoic acid caused reductions in metabolites downstream of ACL (acetyl-CoA, malonyl-CoA, and HMG-CoA) with concomitant increases in ACL substrate (citrate).
- In a cell-free system, ETC-1002-CoA, but not the parent molecule, directly inhibited recombinant human ACL in a concentration dependent manner (K_i =2μM), while ETC-1002 was inactive.
- Bempedoic acid demonstrated potent inhibition of de novo lipid synthesis in vitro upon incubation with primary human hepatocytes with a mean IC_{50} of 9.7μM.
- In vitro studies in primary rat hepatocytes demonstrated that bempedoic acid suppressed lipid synthesis (the incorporation of [^{14}C]-acetate into sterols), with IC_{50} values ranging from of 3 to 10μM.
- In both primary human hepatocytes and RH7777 cells, inhibition of lipid synthesis by bempedoic acid and genetic silencing of ACL led to a 50% upregulation of LDLR protein and a greater than 2-fold increase in LDLR activity. Bempedoic acid also induced a compensatory upregulation of key cholesterol-regulating genes including SREBP2, HMG-CoA reductase, and proprotein convertase subtilisin/kexin type 9 (PCSK9).
- ACSLV1's role in activation of ETC-1002 to ETC-1002-CoA was confirmed by the lack of detectable levels of ETC-1002-CoA in tissues known not to express ACSVL1 (e.g., skeletal muscle) and the absence of ETC-1002-CoA formation and activity in liver cells in which ASCLV1 expression is ablated through gene mediated silencing**.**

In Vivo Activity Related to Proposed Indication

- In apolipoprotein E knockout ($Apoe^{-/-}$) mice fed a HFHC, treatment with bempedoic acid at 30 mg/kg for 14 days resulted in lower plasma LDL-C (60%) but increased plasma very LDL-C and HDL-C levels.

- In diet-induced dyslipidemic male Golden Syrian hamsters, treatment with bempedoic acid at 30 mg/kg/day for 30 days resulted in significant reductions in plasma LDL-C (24% to 38%) and very LDL-C (25% to 64%) and lowered plasma cholesterol (77%) and triglycerides (41%). Further reductions in hepatic triglycerides (34% to 64%), cholesteryl esters (18% to 67%) and free cholesterol (18% to 31%) were noted at 3 mg/kg/day or greater doses.
- The ability of bempedoic acid to prevent diet-induced increases in total plasma cholesterol and LDL-C, and to attenuate atherosclerosis was evaluated in Yucatan miniature pigs heterozygous ($LDLR^{+/-}$) or homozygous ($LDLR^{-/-}$) for deficiency of the LDLR. Long-term treatment (160 days) with bempedoic acid at 120 and 240 mg/kg resulted in significant decreases in LDL-C levels (54% to 63%) in $LDLR^{+/-}$ pigs; modest decreases (27% to 29%) in LDL-C were noted in $LDLR^{-/-}$ pigs as compared to vehicle control. Bempedoic acid also decreased the total area of aortic lesions by 58% and 47% in $LDLR^{+/-}$ and $LDLR^{-/-}$ pigs, respectively.

13.1.1.2. Secondary Pharmacology

- In cell-based in vitro binding and transactivation assays, both bempedoic acid and its active metabolite (ESP15228) demonstrated weak interaction with human PPARα and PPARγ at concentrations greater than 100μM. No binding or activation of PPARδ was observed. Further, biochemical, microscopic and ultrastructural evidence of peroxisome proliferation consistent with PPAR agonism were observed in rodent studies across all treatment durations and monkey short term studies. PPARα activation is not considered a relevant target for the pharmacodynamic action of bempedoic acid in humans based on the absence of clinically meaningful changes on plasma lipids and glucose that are associated with PPARα and PPARγ activation, respectively, as well as the minimal activity noted at those receptors as compared to marketed PPARα and PPARγ agonists.
- In vitro mechanistic and in vivo rodent studies showed that bempedoic acid activates adenosine monophosphate-activated protein kinase (AMPK). AMPK is a heterotrimeric complex composed of a catalytic α subunit and regulatory β and γ subunits that is highly conserved metabolic sensor of cellular energy through inhibition of phosphorylation of acetyl-CoA carboxylase and HMG-CoA reductase, resulting in reduced glucose and lipid biosynthesis.
- In a mechanistic cell-free AMPK activity assays, ETC-1002-CoA activated recombinant human AMPKαβγ complexes in a β1-dependent manner. AMPKβ2 predominates in human liver whereas mouse liver expresses the AMPK β1 isoform. Therefore, AMPK activation by bempedoic acid may be a rodent-specific finding, and remains of unclear human relevance. In addition, using a HFHC fed *Apoe/Ampk β1* double-knockout mice, it was established that the pharmacodynamic effect of bempedoic acid (i.e., plasma LDL-C lowering) can occur independently of AMPK status.
- Bempedoic acid did not show off-target binding when screened against a panel of 54 receptors, ion channels and enzymes.
- Both bempedoic acid and its CoA thioester conjugate failed to inhibit microsomal HMG-CoA reductase.

13.1.1.3. Safety Pharmacology

Based on safety pharmacology studies conducted to assess the potential for cardiovascular, neurobehavioral, and respiratory effects, bempedoic acid did not appear to pose any acute safety concerns at clinically relevant exposures.

Table 48. Summary of Safety Pharmacology Studies

Study/ Study No.	Findings
Effects of ETC-1002 on hERG current: RR 1002-500-007	The effect of bempedoic acid on hERG current was tested on HEK293 cells expressing hERG potassium channel at 10, 100, 300 and 1,000μM. Bempedoic acid did not affect hERG channel activity up to 300μM. A statistically significant 5.4% inhibition of the hERG current was noted at 1,000μM, the highest concentration tested. IC_{50} was not calculated but was estimated to be >1,000μM (345 μg/mL), at least 15 times the human C_{max} at the clinical dose of 180 mg.
Potential neurobehavioral effects in male Wistar rats: RR 1002-500-005 Wistar Han rats 10/males/Group 0, 10, 30, 100 mg/kg Oral, single dose	Functional observational battery (FOB) evaluation was conducted in rats administered with single dose of bempedoic acid at predose and at 4 and 24 hours postdose. Bempedoic acid did not have any significant effects on arousal/activity, autonomic, neuromuscular and physiological functions evaluated on this study. Significant decreases in thermal response latency (time to initiate paw lick following hot plate exposure) was observed 4 and 24 hours postdose at 100 mg/kg. These findings may be consistent with a hyperalgesia response. The NOEL for nervous system function is 30 mg/kg1 (4 and 5 times the human C_{max} and AUC at the clinical dose of 180 mg, respectively.).
Potential Cardiovascular effects in male cynomolgus monkeys: RR 1002-500-004 Cynomolgus monkeys 4/males/Group 0, 10, 30, 100 mg/kg Oral, single dose	Cardiovascular parameters (heart rate, blood pressure, and electrocardiograms) were monitored in monkeys administered single dose of bempedoic acid 2 hours predose until at least 20 hours postdose. Administration of bempedoic acid up to 100 mg/kg in telemetered monkeys did not produce any significant changes on heart rate, blood pressure (systolic, diastolic, mean arterial), or ECG parameters (QRS duration, PR, RR and QT intervals). The NOEL for cardiovascular function is established as highest dose tested 100 mg/kg2 (13 and 19 times human C_{max} and AUC at the clinical dose of 180 mg, respectively).
RR 1002-500-003: Potential pulmonary effects in male Wistar rats Wistar Han rats 8/males/Group Dose: 0, 10, 30, 100 mg/kg Oral, single dose	Pulmonary function was assessed in rats given single dose of bempedoic acid in rats 1 hour predose and 6 hours postdose using whole-body plethysmograph. There were no drug-related effects on respiratory rate, tidal volume and minute volume. The NOEL is the highest dose tested 100 mg/ kg1 (13 and 18 times the human C_{max} and AUC at the clinical dose of 180 mg, respectively).

[1] No PK data; based on 4-week rat study in rats (RR 1002-500-001)
[2] No PK data; based on 14-day monkey study (RR 55016-500-006)
Systemic exposures ($AUC_{0\text{-}24h}$ and C_{max} are combined sex ETC-1002 + ESP15228. Exposure multiples were based on population pharmacokinetics analysis from phase 3 trials in which the maximum clinical dose resulted in systemic geometric mean combined ETC-1002 and ESP15228 exposures $AUC_{0\text{-}24hr}$ and C_{max} of 340 μg.hr/mL and 23.4 μg/mL.
Abbreviations: ECG, electrocardiogram; hERG, human ether-a-go-go-related gene; IC_{50}, concentration inhibiting 50% activity; NOEL, no observed effect level

13.1.1.4. ADME/PK

Bempedoic acid ADME and PK parameters were characterized in human, rats, monkeys, and rabbits.

Absorption

- Absolute and relative bioavailability were not measured in nonclinical species. The bioavailability inferred from recovery of radioactivity in the bile of bile duct–cannulated rats suggest that approximately >86% of oral dose was absorbed after a single dose administration.
- An oral dose of bempedoic acid is rapidly absorbed and T_{max} was achieved within 1 to 2 hours in rats and monkeys and 4 hours in rabbits and 3.5 hours in humans.
- It has a relatively long half-life ($t_{1/2}$) of 18 hours in rats and monkey, 10 hours in rabbits, and 19 hours in humans.

Table 49. Comparison of Bempedoic Acid PK Parameters Across Nonclinical Species, Absorption After a Single Dose

			Test Article: Bempedoic Acid			
Species	Rat		Rat (intact and bile duct-cannulated)			
Study Number	15228-500-03		RR 1002-500-031			
Gender (M/F)/Number of animals:	M/9		M/3			
Feeding condition:	Fed		Fed			
Drug Lot:	Batch AL163-59		Batch 70849-7-28; ^{14}C Batch: 54076-15-18 (6.88-7.73 x 10^5 Bq/mg])			
Vehicle/Formulation:	0.5% CMC		0.5% CMC			
Method of Administration:	Oral gavage		Oral gavage			
Dose (mg/kg):	100		10			
Sample (eg, whole blood, plasma, serum):	Serum (ETC-1002); plasma (ESP15228)		Plasma, whole blood			
Analytes:	ETC-1002, ESP15228		Radioactivity (ETC-1002 equivalents)			
Assay:	LC-MS/MS		Liquid scintillation counting			
			Intact		**Bile duct-cannulated**	
PK parameters:	**ETC-1002**	**ESP15228**	**Plasma**	**Blood**	**Plasma**	**Blood**
t_{max} (hour)	8.00	8.00	2.00	2.00	2.00	2.00
C_{max} (µg/mL or µg equivalent/mL)	619	427	19.4	11.1	16.7	7.38
AUC_t (µg·hr/mL or µg equivalent·hr/mL)	26200	16600	186	105	113	54.4
AUC_∞ (µg·hr/mL or µg equivalent·hr/mL)	NR	NR	186	106	113	46.5
$t_{½}$ (hour)	27.0	11.0	17.9	26.8	4.59	5.14
Blood:Plasma ratio[a]	NA	NA	0.57		0.41	
% Enterohepatic recirculation[b]	NA	NA	39.1			
Location in CTD:	4.2.2.2		4.2.2.2			

Source: Excerpted from the Applicant's submission
[a] AUC_∞ (blood)/AUC_∞ (plasma)
[b] 100 – [AUC_∞ (cannulated)/AUC_∞ (intact)] × 100
Abbreviations: CMC, carboxymethylcellulose; CTD, common technical document; LC, liquid chromatography; LC-MS/MS, liquid chromatography-tandem mass spectrometry; NA, not applicable; NR, not reported; PK, pharmacokinetics; $t_{1/2}$, half-life; t_{max}, time of maximum observed concentration

Distribution

- In vitro plasma protein-binding of bempedoic acid was >95% in mouse, rat, monkey, and human plasma.
- There was no preferential partitioning to red blood cells, and drug-related radioactivity remained primarily in the plasma fraction in all species tested.
- In autoradiography tissue distribution studies in albino and pigmented rats, maximal blood and tissue levels were attained 2 hours postdose. Highest concentrations were observed in gastric and intestinal content, kidney (tissues associated with absorption and elimination), and liver (main site of pharmacological activity).
- There was no evidence of retention in, or affinity for, melanin-containing tissues.

Table 50. In Vitro Protein Binding of Bempedoic Acid in Plasma From Different Species

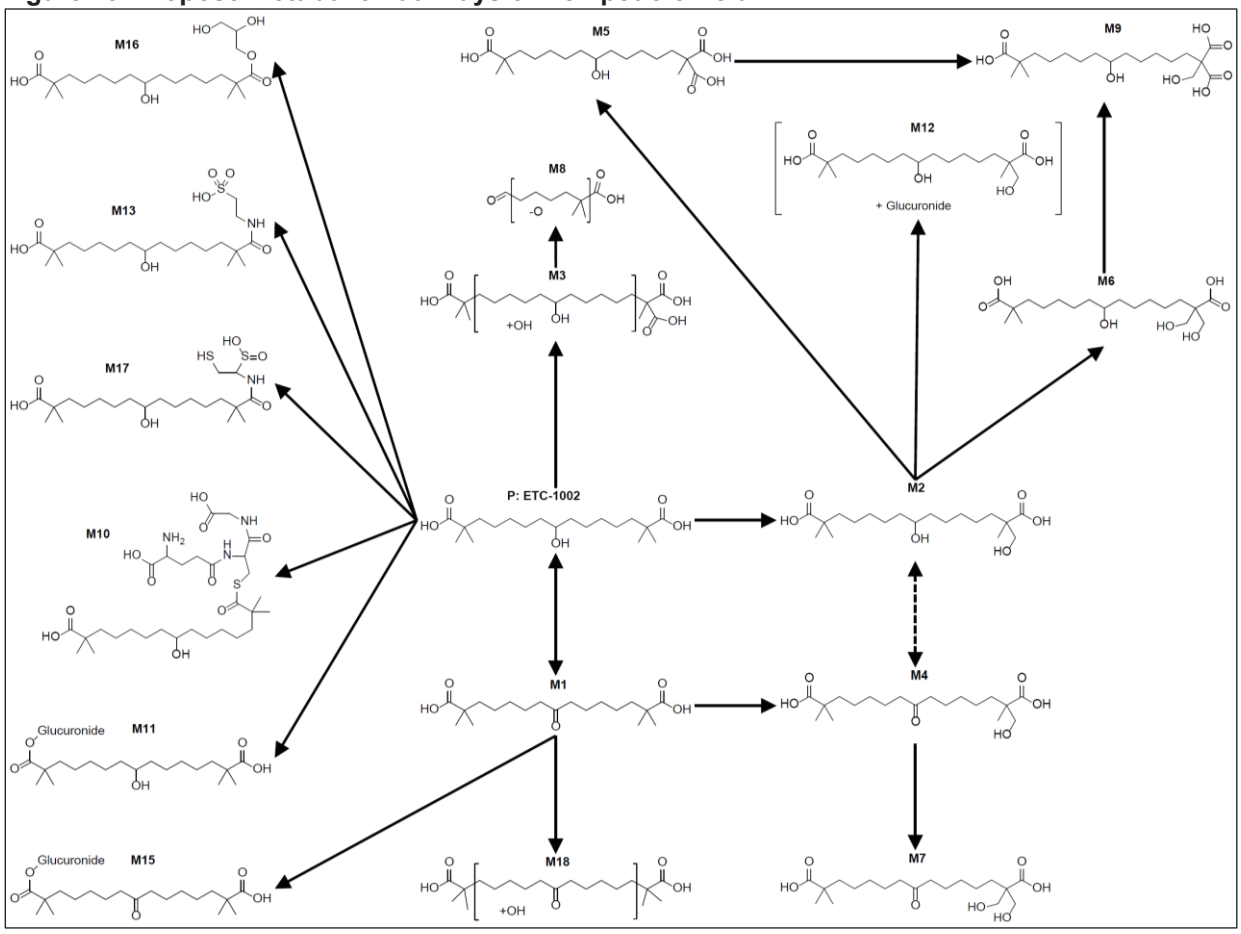
Species	Mean Percent ^{14}C-Bempedoic Acid Bound				
^{14}C-Bempedoic acid concentration:	3 µg/mL	10 µg/mL	30 µg/mL	100 µg/mL	300 µg/mL
Mouse	96.0	96.0	95.0	94.1	86.0
Rat	96.0	95.4	95.0	93.6	86.1
Monkey	97.2	97.0	97.2	96.7	94.7
Human	97.4	97.4	96.8	95.4	91.6

Source: Excerpted from the Applicant's submission

Metabolism

- In general, in vitro and in vivo metabolism studies indicated that the metabolic disposition of bempedoic acid is similar between nonclinical species and humans, and no unique human metabolite was identified.
- Bempedoic acid is primarily metabolized to an inactive glucuronide conjugate (ETC-1002-glucuronide; designated M11) via uridine 5'-diphospho-glucuronosyltransferase 2B7 (UGT2B7). It undergoes reversible oxidation to form an active ketone (ESP15228; designated M1) by aldo-keto reductase in the in vitro (hepatocyte or microsome) preparations and in nonclinical species including humans.
- ESP15228 is pharmacologically active with equivalent potency to ETC-1002. ETC-1002 and ESP15228 exposures were combined for safety margin calculations in this review.
- ESP15228 is further metabolized to inactive metabolite ESP15228-glucuronide conjugate (M15).
- Bempedoic acid analytes: ETC-1002 (parent), ESP15288 (M1), ETC1002-glucuronide conjugate (M11) and ESP15228-glucuronide conjugate (M15) are all detected in human plasma. By comparison, ETC-1002 (parent) accounted for 46% of total AUC, with M11 being the next most prevalent (30%). M1 and M15 accounted for 10% and 11% of AUC, respectively.

Figure 19. Propose Metabolic Pathways of Bempedoic Acid



Source: Excerpted from the Applicant's submission

Excretion

- Bempedoic acid is primarily renally excreted in monkeys (86%) and in humans (70%).
- In bile duct–cannulated rats, biliary excretion was the major route of clearance (86%) and only 5% was eliminated in the urine.
- In intact rats, approximately 78% of the administered dose is excreted in the feces, while only 17% is recovered in the urine.

13.1.1.5. Toxicokinetic Data

Toxicokinetics of bempedoic acid were evaluated in repeat-dose toxicity studies in rats and monkeys; developmental and reproductive toxicology studies in rats and rabbits; and 2-week stand-alone toxicokinetic (TK) studies in mice and rats at dose levels used in 2-year carcinogenicity studies.

Table 51. TK Data From General Toxicity, Reproductive and Carcinogenicity Studies

Study/Study No.	Major Findings
General toxicology studies	
RR 1002-500-038: 26-week repeat-dose oral toxicity study in rats Sample collection times: Predose and at 1, 4, 8, 12, and 24 hours postdose Accumulation: None Dose proportionality: Greater than Sex differences: None ***NOAEL: 10 mg/kg/day*** ***Safety Margin:<1***	**Table 52. TK Parameters for ETC-1002 and ESP15228 in the Rat 26-Week Study**
RR 1002-500-037: 52-week repeat-dose oral toxicity study in monkeys Sample collection times: Predose and at 1, 4, 8, 12, and 24 hours postdose Accumulation: ~2-fold Dose proportionality: Greater than Sex differences: None ***NOAEL: 60 mg/kg/day*** ***Safety Margin: 13***	**Table 53. TK Parameters for ETC-1002 and ESP15228 in the Monkey 52-Week Study**

Bempedoic Acid Dose (mg/kg/day)	ETC-1002				ESP15228			
	C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)		C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 1								
10	15.9	24.6	134	132	1.41	0.544	13.1	5.43
30	89.3	117	1110	1140	7.98	3.54	142	60.8
60	188	193	3380	3250	20.9	11.1	374	165
Day 180								
10	8.19	11.1	42.1	67.9	0.530	0.447	3.14	3.84
30	48.6	76.5	428	544	6.43	3.50	55.0	29.4
60	203	222	1850	2970	10.1	9.33	141	156

Bempedoic Acid Dose (mg/kg/day)	ETC-1002				ESP15228			
	C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)		C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 1								
6	9.58	11.4	84.0	90.6	0.727	0.781	9.88	11.8
20	47.0	41.0	420	410	7.31	3.58	101	59.3
60	201	197	2300	1890	12.6	22.3	209	377
Day 180								
6	8.91	11.7	102	163	0.789	1.43	10.9	22.4
20	53.6	42.6	662	515	13.5	4.82	208	66.6
60	212	274	3240	4000	25.1	48.2	455	870
Day 365								
6	14.3	16.6	149	180	1.37	2.13	18.0	29.9
20	46.5	56.6	703	628	12.8	8.12	209	104
60	311	327	3650	3880	30.7	50.0	555	881

Study/Study No.	Major Findings
Reproductive toxicology studies	
RR 1002-500-041: Oral embryo-fetal developmental toxicity study in rats ***NOAEL: 30 mg/kg/day*** ***Safety Margin: 4***	**Table 54. TK Parameters for ETC-1002 and ESP15228 in the Rat EFD Study, GD 6 and 17**

Bempedoic Acid Dose (mg/kg/day)	Gestation Day	ETC-1002		ESP15228	
		C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)
10	6	22.4	172	0.695	7.46
	17	10.6	72.9	0.585	5.36
30	6	122	1260	3.60	54.3
	17	123	1330	6.76	88.3
60	6	242	3650	8.27	150
	17	220	3610	9.17	180

RR 1002-500-044: Oral embryo-fetal developmental toxicity and toxicokinetic study in rabbits ***NOAEL: 80 mg/kg/day*** ***Safety Margin: 12***	**Table 55. TK Parameters in the Rabbit EFD Study, GD 6 and 18**

Bempedoic Acid Dose (mg/kg/day)	Gestation Day	ETC-1002		ESP15228	
		C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)
20	6	34.3	190	0.464	3.13
	18	48.7	394	0.849	8.02
50	6	102	654	1.20	9.85
	18	134	1160	3.11	25.8
80	6	254	1910	3.81	33.9
	18	292	3770	9.41	136

RR 1002-500-055: Oral rat juvenile toxicity and toxicokinetic study ***NOAEL: 10 mg/kg/day*** ***Safety Margin: 0.2***	**Table 56. TK Parameters in Juvenile Rat Toxicity Study, PND 15, 28 and 90**

Bempedoic Acid Dose (mg/kg/day)	ETC-1002				ESP15228			
	C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)		C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 1 (PND 15)								
1	0.842	1.08	4.67	NA[a]	0.016	0.025	NA[a]	0.149
3	3.99	4.15	42.4	NA[a]	0.106	0.186	NA[a]	NA[a]
10	21.5	22.4	381	410	0.933	1.09	15.7	17.8
Day 14 (PND 28)								
1	0.133	0.110	NA[b]	NA[b]	0.000	0.004	NA[b]	NA[b]
3	2.18	1.42	6.49	7.46	0.163	0.103	NA[b]	NA[b]
10	12.8	13.7	NA[a]	NA[a]	0.696	0.759	NA[a]	NA[a]
Day 76 (PND 90)								
1	0.107	0.217	NA[b]	0.616	0.000	0.009	NA[b]	NA[b]
3	1.85	1.94	4.44	7.43	0.091	0.070	NA[a]	0.291
10	11.5	13.0	55.1	61.8	0.853	0.506	4.66	3.30

From RR 1002-500-055
AUC_{0-24} = Area under the concentration-time curve from 0 to 24 hours postdose; C_{max} = Maximum observed concentration; ETC-1002 = Bempedoic acid; ESP15228 = Phase 1 keto-metabolite of bempedoic acid; NA = Not applicable; PND = Postnatal Day.
[a] Value not reported when percent AUC_{0-24} extrapolation is >25%.
[b] Value not reported due to less than 3 consecutive quantifiable concentrations.

Study/Study No.	Major Findings
Carcinogenicity studies	
RR 1002-500-050: 2-week TK mice study (at doses used in the 2-year mice carcinogenicity study) ***NOAEL: 25 mg/kg/day*** ***AUC: 85.5 µg.h/mL*** ***Safety margin: 0.2***	**Table 57. Toxicokinetic Parameters for ETC-1002 and ESP15228 in the Mice 2-Week Study at Dose Used for Carcinogenicity Study**

Bempedoic Acid Dose (mg/kg/day)	ETC-1002				ESP15228			
	C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)		C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 14								
25	7.26	8.52	67.9	95.8	0.215	0.298	2.79	4.43
75	23.3	32.8	269	390	0.643	1.18	10.0	21.0
150	55.8	67.4	628	1040	1.43	2.96	24.0	54.9

RR 1002-500-049: 2-week TK rat study (at doses used in the 2-year rat carcinogenicity study)

NOAEL: 10 mg/kg/day
AUC: 67.3 µg.h/mL
Safety margin: 0.2

Table 58. Toxicokinetic Parameters for ETC-1002 and ESP15228 in the Rat 2-Week Study at Dose Used for Carcinogenicity Study

Bempedoic Acid Dose (mg/kg/day)	ETC-1002				ESP15228			
	C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)		C_{max} (µg/mL)		AUC_{0-24} (µg·hr/mL)	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 14								
3	1.03	3.60	2.60	10.4	0.053	0.085	0.144	0.333
10	11.5	12.2	57.6	70.2	0.646	0.485	3.66	3.21
30	65.7	112	433	1500	3.50	5.19	29.7	81.7

Safety margins were based on population pharmacokinetics analysis from phase 3 trials, where the maximum clinical dose resulted in systemic geometric mean combined ETC-1002 and ESP15228 exposures (AUC_{0-24hr}) of 340 µg.hr/mL.
Abbreviations: EFD, embryo-fetal development; GD, gestation day; PND, postnatal day; NOAEL, no observed adverse effect level; TK, toxicokinetics

13.1.1.6. Toxicology

13.1.1.6.1. General Toxicology

13.1.1.6.1.1. 26-Week Oral Toxicity Study in Rats / RR 1002-500-038

Key Study Findings

- Mortality occurred in one toxicokinetic female treated at 60 mg/kg/day due to bempedoic acid–related severe hepatocyte necrosis in the liver.
- Targets and target organs of toxicity were RBC mass, the liver, and the kidney.
- Consistent with findings in shorter-term studies, bempedoic acid caused mildly (5% to 15%) reduced RBC mass, including decreases in Hgb, Hct, mean corpuscular volume, and mean cell Hgb at ≥10 mg/kg/day and reticulocytes at ≥30 mg/kg/day in both sexes. No correlative effects were noted upon analysis of bone marrow histology and smears, and no evidence of increased RBC consumption or hemolysis were seen.
- In the liver, bempedoic acid caused minimal hepatocyte necrosis at ≥30 mg/kg in females and 60 mg/kg in males, minimal subcapsular necrosis in one male at 60 mg/kg/day, minimal to severe centrilobular vacuolation in both sexes at ≥30 mg/kg, bile duct hyperplasia in males only at 60 mg/kg, and increases in brown pigment, which were not iron reactive in males and females at all doses. These histological changes occurred concomitantly with elevation of LFTs and total bilirubin predominantly at highest dose tested 60 mg/kg/day. Vacuolation correlated with increased hepatocellular lipid content (positive staining for Oil Red O).

- In addition, treatment with bempedoic acid caused dose-related increases in absolute and relative liver weights (23% to 154%) and minimal to moderate centrilobular to panlobular hepatocellular hypertrophy in both sexes at ≥10 mg/kg/day. These liver changes are attributable to bempedoic acid's PPARα activity as evidenced by electron microscopy findings of qualitative increases in liver peroxisome at all doses.
- In the kidney, dose-related nonadverse minimal to mild brown tubular pigment (cortex) that was not iron reactive were observed ≥10 mg/kg/day in both sexes.
- The NOAEL was established as 10 mg/kg/day (below the clinical exposure at the human dose of 180 mg dose, based on AUC). The NOAEL was based on adverse liver hepatocyte necrosis and ≥93% increases in liver weight in animals treated at ≥30 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 59. Methods of 26-Week Oral Toxicity Study in Rats

Study Feature	Method Details
Dose and frequency of dosing	0 (vehicle), 10, 30 and 60 mg/kg/day, once daily for 26 weeks
Route of administration	Oral gavage
Formulation/vehicle	0.5% carboxymethylcellulose in distilled water
Species/strain	Rat/Wistar Han (b) (4)
Number/sex/group	15/sex/group
Age	8 weeks at initiation
Satellite groups/unique design	TK Additional end points were included to assess PPAR-related toxicities including, cardiac and skeletal muscle troponins, histomorphometry measurements, Oil Red O staining, quantification of peroxisomal enzymes, proliferation, ultrastructural changes, transmission electron microscopy were conducted in the liver and heart samples as appropriate.
Deviation from study protocol affecting interpretation of results	None

Abbreviations: PPAR, peroxisome proliferator-activated receptor; TK, toxicokinetics

Table 60. Observations and Results of 26-Week Oral Toxicity Study in Rats

Parameter	Major Findings
Mortality	Three deaths (one drug-related and two nondrug-related) Control: One male was found dead on Day 121 due to hemangiosarcoma (not drug-related). HD: One TK female was euthanized in extremis on Day 86. The cause of moribundity was with severe individual hepatocyte necrosis of the liver. Additional findings in the liver include mild panlobular hypertrophy and minimal periportal vacuolation. Death is considered drug-related based on the hepatic findings in other HD animals. HD: One main study male was euthanized in extremis on Day 114. Calculi were noted in the urinary bladder and inflammation was present within the urinary bladder, prostate and renal pelvis. The cause of death was urogenital inflammation due to calculi and considered not drug-related.

Parameter	Major Findings
Clinical signs	Unremarkable
Body weights	Males: Dose-dependent decreases in body weight (2%–10%) and gain (5%–18%) were observed. Females: Animals treated at MD and HD had 4 and 7% decreases in body weight and 12 and 22% lower body weight gains, respectively. The body weight effects were considered test article-related, but not adverse. Food consumption was not affected in this study.
Ophthalmoscopy	LD: One female rat had a cataract in the R eye, and another female rat present with chorionretinal hypoplasia in the L eye. Findings are considered incidental because of the low incidence and absence of a dose response.
ECG	N/A
Hematology	All doses: Non-dose related ↓ hemoglobin (5%–15%), hematocrit (14%), MCV (4%–12%), MCH (4%–13%). Reticulocyte counts were lower by up to 17% females at MD and HD. Changes in hematology were apparent on Week 6, 17 and termination. There were no correlating changes observed in bone marrow both by bone marrow smears and histological analysis and spleen. MD and HD: 28%–40% ↑ lymphocytes and 35%–156% ↑ in monocytes; occurred in the absence of inflammatory changes
Coagulation	MD and HD: ↓ APTT (17%–38%) and PT (5%–7%); unknown significance
Clinical chemistry	HD: increases in ALP (3.6x), ALT (2.4x), AST (2.2x), TB (3.4x), GGT (2.6x) All doses: increases in urea nitrogen (up to 16%), TP (up to 16%), albumin (up to 24%), globulin (up to 8%)
Urinalysis	All doses: ↑ urine pH (3%–9%)
Gross pathology	There were no test article-related macroscopic findings.
Organ weights	All doses: ↑ in absolute (22%–130%) and relative (23%–153%) liver weight
Histopathology Adequate battery: Yes	Liver: Adverse drug-related minimal hepatocyte necrosis in HD males and females at MD and HD, minimal subcapsular necrosis in HD male, bile duct hyperplasia in HD males, nonadverse minimal to moderate centrilobular to panlobular hepatocellular hypertrophy at all does, minimal to mild vacuolation in HD males, minimal to mild increases in pigment (not iron reactive) in MD and HD males and in females at all doses. One female TK died due to severe hepatocyte necrosis. Kidney: Nonadverse dose-related minimal to mild tubular pigment within the cytoplasm of tubular epithelial cells that was not iron reactive occurred at all doses. Lung: Increased incidence of minimal lung alveolar histiocytosis in MD and HD males but was not thought to be test article related rather linked to drug aspiration into lungs. There were no dose-response and similar finding present in females.
Special Evaluations	
Electron microscopy	Increased liver peroxisomal content at all doses and increased lipid content in the liver at HD
Oil-Red-O staining	Positive staining for Oil-Red-O (lipids) in the hepatocytes of HD animals
Cardiac histomorphometry	Unremarkable
Bone marrow cytology	Unremarkable

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT, activated partial thromboplastin time; GGT, gamma-glutamyl transferase; HD, high dose; LD, low dose; MCH, mean cell hemoglobin; MCV, mean corpuscular volume; MD, mid-dose; N/A, not applicable; PT, prothrombin time; TB, total bilirubin; TK, toxicokinetics; TP, total protein

13.1.1.6.1.2. 52-Week Oral Toxicity Study in Monkeys RR 1002-500-037

Key Study Findings

- Bempedoic acid produced mild increases (up to 62%) in creatinine in both sexes treated at ≥20 mg/kg/day without any correlating histological kidney changes. Higher creatinine levels were apparent as early as 13 weeks of treatment in females. The increase in creatinine might be attributed to ETC-1002 mediated inhibition of OAT2, a transporter mediating the secretion of creatinine in the kidney.
- Electron microscopy showed qualitatively increased peroxisomes in the liver in all treated females and MD and high dose (HD) males. However, the peroxisomal proliferation occurred in the absence of correlative increase in liver weight and adverse histological changes.
- There was diffuse or periportal vacuolation of hepatocytes present in the liver of MD and HD animals, which stained positive (mild) for Oil Red O staining (lipid content) in the liver. Nevertheless, these changes were not considered adverse, and due to the absence of frank toxicity, the NOAEL was established as 60 mg/kg/day (13 times the clinical exposure at the human dose of 180 mg, based on AUC).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Study Information

Table 61. Methods of 52-Week Oral Toxicity Study in Monkeys

Study Feature	Method Details
Dose and frequency of dosing	0 (vehicle), 6, 20 and 60 mg/kg/day, once daily for 52 weeks
Route of administration	Oral gavage
Formulation/vehicle	0.5% carboxymethylcellulose in distilled water
Species/strain	Monkey/Cynomolgus monkey
Number/sex/group	4/sex/group
Age	2 to 4 years at transfer
Satellite groups/ unique design	TK/ Additional end points to assess PPAR-related toxicities were included.
Deviation from study protocol affecting interpretation of results	None

Abbreviations: PPAR, peroxisome proliferator-activated receptor; TK, toxicokinetics

Table 62. Observations and Results of 52-Week Oral Toxicity Study in Monkeys

Parameter	Major Findings
Mortality	None
Clinical signs	There were imbalances for the incidences of emesis. However, the majority of the observations were related to only a very few animals and were ultimately not considered drug-related.
Body weights	Mean body weight gain was decreased by 40% and 51% in MD and HD females as compared to the controls, respectively. In males, mean body weight gain was decreased by 17% in HD males only. The decrement in body weight gain correlated to decreases in absolute mean body weights of 13% and 15% in MD and HD females, respectively and 7% in HD males.
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	Non-dose dependent mild increases (13%–64%) in APTT were noted in both sexes at all doses. APTT prolongation was observed by Week 13 at MD and HD and all doses at termination. No change in RBC mass and bone marrow evaluation (smears) were observed.
Clinical chemistry	Creatinine was increased (up to 62%) at termination in both sexes at MD and HD. The increase in creatine was evident starting from Week 13 in MD and HD females and HD males. The increases in creatinine lacked microscopic correlates. As expected from pharmacology of bempedoic acid, there were decreases in cholesterol (15%–52%) at Week 13 and termination in males and females at MD and HD. Increase in FFA (13%) in HD males and all dosed females (up to 122%).
Urinalysis	Unremarkable
Gross pathology	Unremarkable
Organ weights	Unremarkable
Histopathology Adequate battery: Yes	Liver: Minimal to mild periportal and diffuse vacuolation in MD and HD males and HD females
Special Evaluation	
Electron microscopy (TEM)	Qualitative increases in the number of peroxisomes in the liver of all treated females and MD and HD males. Increase in lipid content in the liver and heart in MD and HD males and females.
Oil-Red-O staining	There was increased severity of positive Oil-Red-O staining (lipid content) in the heart and liver of MD and HD females (from minimal in control and LD to mild or moderate in MD and HD groups).
Cardiac histomorphometry	Unremarkable
Bone marrow cytology	Unremarkable

Abbreviations: APTT, activated partial thromboplastin time; ECG, electrocardiogram; FFA, free fatty acids; HD, high dose; LD, low dose; MD, mid-dose; RBC, red blood count; TEM, transmission electron microscopy

13.1.1.6.2. Genetic Toxicology

The Applicant completed a battery of in vitro and in vivo genotoxicity study with bempedoic acid.

Table 63. Genotoxicity Studies

Study Title/Study No.	Key Study Findings
In Vitro Reverse Mutation Assay in Bacterial cells/55016-500-3 GLP compliance: Yes Study is valid: Yes	Bempedoic acid was tested in four strains of *Salmonella typhimurium* strains (TA98, TA100, TA1535 and TA1537) and *Escherichia coli* strain (WP2 uvrA) at 100 to 5,000 µg/plate concentration with and without S9 metabolic activation. Negative: No mutagenicity, precipitate or toxicity were observed in any strain at all tested doses with or without metabolic activation.
Chromosomal Aberrations Assay In Vitro in the Human Peripheral Blood Lymphocytes (HPBL)/ 55016-500-004 GLP compliance: Yes Study is valid: Yes	HPBL were exposed to bempedoic acid for 3 hours at 50, 500, 1,000 µg/mL with metabolic activation and at 50, 500, and 1,250 µg/mL without metabolic activation. Positive: Clastogenic response was observed with metabolic activation at the highest concentration tested (1,000 µg/mL). However, this response was considered not biologically relevant since 1,000 µg/mL concentration cytotoxic (relative mitotic index = 58%).
In Vivo Mouse Micronucleus Assay/55016-500-013 GLP compliance: Yes Study is valid: MTD was not achieved	Group of CD-1 mice (10/sex/dose) were given bempedoic acid at a single oral dose of 500, 1,000, and 2,000 mg/kg (actual dose: 184.5, 510 and 1,242 mg/kg). The highest dose was devoid of any toxicity in the DRF study. Of this, 5/sex/dose were euthanized either after 24 or 48 hours postdose. Femoral bone marrow was harvested, and 2,000 PCE were examined for the presence of MN PCE. Negative: There was no increase in MN PCE in the bone marrow up to 1,242 mg/kg dose. No bone marrow cytotoxicity was observed.
In vivo Rat Micronucleus and Liver Comet Assays/55016-500-008 GLP compliance: Yes Study is valid: Yes	Bempedoic acid was administered to a group of Wistar rats (5/male/dose) orally at 10, 30, and 100 mg/kg doses for 2 consecutive days. The high dose was associated with mortality in male rats (Study # RR 1002-500-001). Approximately 3 hours after the second daily dose, animals were euthanized, and bone marrow and liver were collected, processed, and assessed for MN PCE and DNA damage (comet assay), respectively Negative: Bempedoic acid did not increase MN PCE in bone marrow or induce DNA damage in the liver.

Abbreviations: DRF, Dose-range–finding study; GLP, good laboratory practice; MTD, maximum tolerated dose; MN PCE, micronucleate polychromatic erythrocytes

13.1.1.6.3. Carcinogenicity

13.1.1.6.3.1. 104-Week Oral Carcinogenicity Study in Rat (RR 1002-500-035)

Wistar Han rats (65/sex/group) were administered with vehicle (0.5% w/v carboxymethylcellulose sodium salt) or bempedoic acid at 3, 10, and 30 mg/kg/day by oral gavage for 104 weeks. Doses were selected based on maximum tolerated dose (MTD) (reduced body weight gain in males and mortality at 100 mg/kg/day in both sexes). All dose groups were terminated at Week 104, as originally planned. Treatment with bempedoic acid did not affect survival of either males or females. Drug exposure was confirmed in satellite toxicokinetic animals at Weeks 26 and 52 in both sexes.

Key Study Findings

- Liver hepatocellular adenomas and hepatocellular adenomas and carcinomas combined were identified as statistically significant in males at 30 mg/kg/day by using both trend and pairwise comparison. The incidence of liver tumors in high-dose males were higher than reported in the historical control data from the testing facility and was associated with preneoplastic changes in the liver (eosinophilic focus of cellular alteration).
- Thyroid follicular cell adenomas, follicular cell adenomas and carcinomas combined showed statistical significance in males treated at 30 mg/kg/day by trend analysis and pair-wise comparison.
- An independent FDA statistician review also showed statistically (trend, pairwise) increased incidence of pancreatic islet cell adenoma and carcinoma combined in males treated at 30 mg/kg/day. The incidence of pancreatic adenoma and carcinoma combined exceeded the range reported for the historical control from the testing facility and animal supplier. Pancreatic tumor was considered bempedoic acid–related based on statistical significance.
- The Executive Carcinogenicity Assessment Committee concurred that the liver, thyroid and pancreatic tumors in males at 30 mg/kg/day are treatment-related.
- Hepatocellular tumor is an established tumor type of drugs activating PPARα (e.g., fibrates). Bempedoic acid demonstrated weak binding to human and rodent PPARα in the in vitro transactivation assay. It also provoked prototypical PPARα–related liver toxicities including dramatic liver weight increases, hepatocellular hypertrophy, ultrastructural (peroxisomal proliferation), and biochemical change (induction of peroxisomal enzymes) in both rat and mice studies.
- Liver tumor formation is unlikely to be encountered in humans due to the known PPARα mediated species-specific differences between the rat and human for this tumor.
- Thyroid gland neoplasms observed in bempedoic acid–treated males might be secondary to thyroid hormone imbalances. Indeed, circulating levels of total and free T3 and T4 were decreased up to 79% following treatment with bempedoic acid in an exploratory 2-week study in rats (RR 1002-500-025). The relevance of enzyme induction in thyroid tumor development is disputed in humans due to marked species specific differences in susceptibility to thyroid tumors due to thyroid-pituitary perturbation and considered rat specific.
- The cause and human relevance of islet cell pancreatic tumors in male rats are not known.

Table 64. Bempedoic Acid–Related Tumors Identified in Male Rats

Parameter	Incidence, n (%), N=65					Statistical Analysis[3]			
						FDA		Applicant	
Bempedoic acid (mg/kg/day)	0	3	10	30	Historical Control (%)				
Exposure multiple[2]	-	0.008	0.2	1.4	Mean (range)[1]	Trend	Pairwise	Trend	Pairwise
Liver									
Hepatocellular adenoma	0	0	1 (1.5)	7 (11)	1 (0-3.3)	**0.0001**	0.0069 (HD) 0.5169 (MD)	**0.0005**	0.0132 (HD) 1.0000 (MD)
Hepatocellular carcinoma	0	0	1 (1.5)	1 (1.5)	0.34 (0-1.7)	0.1888	0.5043 (HD) 0.5169 (MD)	0.2169	1.0000 (HD) 1.0000 (MD)
Hepatocellular adenoma/carcinoma	0	0	2 (3)	8 (12)	1.34 (0-5)	**0.0000**	0.0032 (HD) 0.2651 (MD)	NC	NC
Thyroid									
Follicular cell adenoma	0	2 (3)	4 (6)	9 (14)	5.2 (3.3-8.2)	**0.0005**	0.0015 (HD) 0.0680 (MD) 0.2565 (LD)	**0.0008**	0.0029 (HD) 0.1192 (MD) 0.4961 (LD)
Follicular cell carcinoma	0	3 (5)	1 (1.5)	3 (5)	2.3 (1.7-3.3)	0.1520	0.1283 (HD) 0.5169 (MD) 0.1283 (LD)	0.2637	0.2442 (HD) 1.0000 (MD) 0.2442 (LD)
Follicular cell adenoma/carcinoma	0	5 (8)	5 (8)	12 (19)	7.5(5-11.5)	**0.0004**	0.0002 (HD) 0.0340 (MD) 0.0312 (LD)	NC	NC
Pancreas									
Islet cell adenoma	1 (1.5)	3 (5)	0	7 (11)	4.8 (1.5-10)	0.0063	0.0322 (HD) 0.5169 (MD) 0.3224 (LD)	0.0484	0.0619 (HD) 1.0000 (MD) 0.6191 (LD)
Islet cell carcinoma	0	1 (1.5)	1 (1.5)	2 (3)	0.53 (0-1.7)	0.1200	0.2522 (HD) 0.5169 (MD) 0.5086 (LD)	0.1949	0.4961 (HD) 1.0000 (MD) 1.0000 (LD)
Islet cell adenoma/carcinoma	1 (1.5)	4 (6)	1 (1.5)	9 (14)	5.3 (1.5-11.7)	**0.0025**	0.0088 (HD) 0.7688 (MD) 0.1930 (LD)	NC	NC

Source: Nonclinical Reviewer
[1] Historical control is shown as % mean incidence (range) from [redacted] (b) (4) Historical Control, Neoplastic Data, Wistar Han Rat, 2-Year Studies, 8/1/2003 to 8/1/2014.
[2] Exposure multiples were based on population pharmacokinetics analysis from phase 3 trials in which the maximum clinical dose resulted in systemic geometric mean combined ETC-1002 and ESP15228 exposures ($AUC_{0\text{-}24hr}$) of 340 µg.hr/mL. Exposure (ETC-1002 + ESP15288) in rat is obtained from the 14-Day oral toxicokinetic study in Wistar rat conducted at the same dose (RR 1002-500-049).
[3] Statistically significant dose-related trend for tumor incidence, p≤0.005 and p≤0.025 for common (background rate >1%) and rare tumor (background rate ≤1%), respectively. Statistically significant difference from control group by pairwise comparison, p≤0.01 and p≤0.05 for common (background rate >1%) and rare (background rate ≤1%) tumors, respectively.
Abbreviations: HD, high-dose; LD, low-dose; MD, mid-dose; N, total number of animals with tumors; n, number of animals with type of tumor; NC, Analysis not conducted

13.1.1.6.3.2. 104-Week Oral Carcinogenicity Study in Mice (RR 1002-500-036)

A group of male and female CD-1 mice (65/sex/group) were administered daily with vehicle (0.5% w/v carboxymethylcellulose sodium salt) or bempedoic acid at 25, 75, and 150 mg/kg/day by oral gavage for 104 weeks. Doses were selected based on MTD (severe liver toxicities which occurred at doses ≥300 mg/kg/day). During Week 42, TK animals were combined with the main study animals due to excessive mortality (skin lesions) in the main study animals. The main study male and female mice were terminated at Weeks 104 (scheduled termination) and 101 (when the MD female group declined to 15 animals), respectively. Males showed a statistically significant dose-related trend for increased mortality, and survival was significantly lower in males at 150 mg/kg/day as compared to vehicle controls. A statistically significant decrease in survival was also reported in females at 75 mg/kg/day; however, this was not considered drug-related based on the absence of dose relationship. Drug exposure was confirmed in satellite toxicokinetic animals at Week 26 in both sexes.

Key Study Findings

- Liver hepatocellular adenomas, hepatocellular carcinomas, and hepatocellular adenomas and carcinomas combined were significantly increased in male mice at 75 and 150 mg/kg/day by both trend and pairwise comparison. The increases in the incidence of liver tumors exceeded the historical control range and were also associated with preneoplastic changes (e.g., basophilic and eosinophilic focus of cellular alteration) and non-neoplastic (centrilobular hepatocellular hypertrophy) in the liver.
- The Executive Carcinogenicity Assessment Committee concurred that the incidence of liver hepatocellular adenomas, hepatocellular carcinomas and combined incidence of hepatocellular adenomas and carcinomas in male mice at 75 and 150 mg/kg/day are drug related.
- Increase in liver tumor is likely be related to well established link between PPARα activation with excessive peroxisomal proliferation and liver tumor in rodents and is consistent with the results of several PPARα agonists. Bempedoic acid-induced liver tumors are not likely to occur in humans on the basis of species-specific differences between mice and humans regarding sensitivity to PPARα agonists.

Table 65. Bempedoic Acid–Related Tumors Identified in Male Mice

Parameter	Incidence, N (%)				Historical control (%) mean (range)[1]	Statistical Analysis[3]			
						FDA		Applicant	
N[4]=	72	77	76	77					
Bempedoic acid (mg/kg/day)	0	25	75	150					
Exposure multiple[2]	-	0.2	0.8	2		Trend	Pairwise	Trend	Pairwise
Liver									
Hepatocellular adenoma	12 (17)	16 (21)	26 (34)	27 (35)	14 (10-15)	**0.0001**	0.0012 (HD) 0.0061 (MD) 0.3945 (LD)	**0.001**	0.0149 (HD) 0.0232 (MD) 0.5377 (LD)
Hepatocellular carcinoma	6 (8)	12 (16)	21 (28)	24 (31)	5 (0-10)	**0.0000**	0.0000 (HD) 0.0005 (MD) 0.1404 (LD)	**<0.0001**	0.0005 (HD) 0.0027 (MD) 0.2132 (LD)
Hepatocellular adenoma/carcinoma	18 (25)	26 (34)	37 (49)	41 (53)	19 (10-25)	**0.0000**	0.0000 (HD) 0.0007 (MD) 0.2045 (LD)	**<0.0001**	0.0005 (HD) 0.0037 (MD) 0.2827 (LD)

Source: Nonclinical Reviewer
[1] Historical control is shown as % mean incidence (range) from (b) (4) Historical Control, Neoplastic Data, CD-1 mice, 2-Year Studies, 8/1/2009 to 8/1/2014.
[2] Exposure multiples were based on population pharmacokinetics analysis from phase 3 trials in which the maximum clinical dose resulted in systemic geometric mean combined ETC-1002 and ESP15228 exposures ($AUC_{0\text{-}24hr}$) of 340 µg.hr/mL. Exposure to ETC-1002 + ESP15288 in mice is obtained from the 14-Day oral toxicokinetic study in CD1 mice (RR 1002-500-050).
[3] Statistically significant dose-related trend for tumor incidence, p≤0.005 and p≤0.025 for common (background rate >1%) and rare (background rate ≤1%) tumor, respectively. Statistically significant difference from control group by pairwise comparison, p≤0.01 and p≤0.05 for common and rare tumors, respectively.
[4] At study initiation, each group consisted of 65 animals/sex.TK animals were combined with the main study animals during Week 42 due to excessive mortality (skin lesions) in the main study animals and resulted in uneven number of animals for analysis.
Abbreviations: HD, high-dose; LD, low-dose; MD, mid-dose; N, total number of animals with tumors; n, number of animals with type of tumor; NC, Analysis not conducted

13.1.1.6.4. Reproductive and Developmental Toxicity

13.1.1.6.4.1. Fertility and Early Embryonic Development to Implantation in Rats/RR 1002-500-039

Key Study Findings

- Administration of bempedoic acid prior to mating and through gestation (females) resulted in parental toxicities (reduced body weight and food consumption) at ≥30 mg/kg/day, decreased reproductive organ weights in males (epididymis, prostate gland, seminal vesicle with coagulating gland and testis) at ≥30 mg/kg/day and in females (ovaries, uterus with cervix) at 60 mg/kg/day.
- In female rats, there were decreases in the number of corpora lutea, litter size, implantation sites, and viable embryos at ≥30 mg/kg/day (4 times clinical exposure at the human dose of 180 mg, based on AUC). There were also changes in estrus cyclicity at 60 mg/kg/day (9 times clinical exposure at the human dose of 180 mg, based on AUC).
- No effect was noted on male fertility in spite of drug-related, statistically significant decreases in sperm count observed at 60 mg/kg/day (9 times clinical exposure at the human dose of 180 mg, based on AUC).
- Male and female mating, fecundity indices, and copulatory interval were not affected at any doses.
- The NOAEL for general (male and female) toxicity was 10 mg/kg/day (below the clinical exposure at the human dose of 180 mg, based on AUC), due to drug-related lower body weight observed in both sexes at ≥30 mg/kg/day.
- The NOAEL for male fertility is 60 mg/kg/day (~7.5 times the clinical exposure at the human dose of 180 mg, based on AUC) considering the absence of direct adverse effect on male mating and fertility at all dose levels tested. The NOAEL for female fertility was 10 mg/kg/day based on adverse reproductive indices including, increase in early embryonic deaths, lower corpora lutea, implants and litter sizes at ≥30 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 66. Methods of Fertility and Early Embryonic Development to Implantation

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 10, 30 and 60 mg/kg/day, Once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% carboxymethylcellulose (sodium salt)
Species/strain	Rat/Wistar Han (b) (4)
Number/sex/group	25/sex/group
Satellite groups	None
Study design	Standard; Females: 14 days prior to mating, during mating and through GD7; Males: 28 days prior to mating, during mating and until prior to scheduled sacrifice (9 weeks total)
Deviation from study protocol affecting interpretation of results	Noted and not considered to have affected the quality or integrity of the study.

Abbreviations: GD, gestation day

Table 67. Observations and Results Fertility and Early Embryonic Development to Implantation

Parameters	Major Findings
Mortality	None
Clinical signs	Few/absent feces and thin appearance were observed in MD and HD males and females, and decreased activity and unkempt appearance, hair discolored (yellow) anogenital region were observed in HD males.
Body weights	Decreased BW in both sexes at MD and HD beginning on Day 4 and continuing to study termination, which corresponds to statistically significant reduction in absolute organ weight (epididymis, prostate gland, seminal vesicle) in MD and HD males. Ovaries and uterus with cervix weights were statistically decreased in HD females; no effect on relative organ weight.
Necropsy findings: Cesarean-section data *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]*	Decreased number of corpora lutea, litter size, implantation sites, viable embryos and litter size were seen at MD and HD, increased preimplantation loss at HD. Drug-related statistically significant increases (42%) in mean estrus cycle length (6.1 days versus 4.3 days in controls) and a corresponding decrease (31%) in number of cycles (2.0 versus 2.89 in controls) were observed in HD females. Total sperm count was significantly decreased by 16% in HD males. No effect on male and female mating, fertility, fecundity indices and copulatory interval was reported at all doses.

Abbreviations: BW, body weight; HD, high dose; MD, mid dose

13.1.1.6.4.2. Embryo-Fetal Developmental Study

13.1.1.6.4.2.1. Developmental Toxicity Study in Rats With Toxicokinetic Evaluation / RR 1002-500-041

Key Study Findings

- Administration of bempedoic acid to pregnant female rats from gestation day 6 to 17 resulted in maternal toxicities (decreases in body weight and food consumption) at ≥30 mg/kg/day.
- There were decreases in the number of viable fetuses, litter size, increased postimplantation loss, and increased total resorptions at 60 mg/kg/day and decreases in fetal body weight at ≥30 mg/kg/day.
- There were increases in findings of fetal skeletal variations, including bent long bones, bent scapula, and incomplete ossification, which were observed across all doses; however, these variations are known to reverse postnatally and are thus considered nonadverse.
- The toxicokinetic evaluation confirmed in pregnant female rat systemic exposure to ETC-1002 and its metabolite ESP15228 during the dosing period.
- The NOAEL for maternal toxicity was 10 mg/kg/day (below the systemic exposure at the human dose of 180 mg, based on AUC) due to reduced body weight and food consumption at ≥30 mg/kg/day. In comparison, the NOAEL for developmental toxicity was 30 mg/kg/day (4 times the clinical exposure at the human dose 180 mg, based on AUC) due to adverse uterine data (low fetus viability, implantation losses and increased resorptions) at 60 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 68. Methods of Oral Embryo-Fetal Developmental Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 10, 30 and 60 mg/kg/day; Once daily; GD 6 to GD 17
Route of administration	Oral gavage
Formulation/vehicle	0.5% carboxymethylcellulose (sodium salt)
Species/strain	Time mated female rats/ Wistar Han (b) (4)
Number/sex/group	25/sex/group
Satellite groups	TK: 3 time-mated females/Control group; 9 time-mated females/dose group
Study design	Standard; Pregnant female Wistar Han rats were dosed from GD 6 to GD 17 and euthanized on GD 20.
Deviation from study protocol affecting interpretation of results	Deviations reported did not affect the interpretation of the study findings.

Abbreviations: GD, gestation day; TK, toxicokinetics

Table 69. Observations and Results of Oral Embryo-Fetal Developmental Study in Rats

Parameters	Major Findings
Mortality	None
Clinical signs	HD: Inappetence and thin appearance occurred in up to three females
Body weights	Reduction of final and adjusted (final body weight minus gravid uterine weight) body weights were observed in females at MD and HD. Mean gestation body weight loss were noted at MD during GD 6 to 18 and at HD during GD 9-12, GD 15-18, GD 6-10 and GD 0-20. BW decrease correlate with lower food consumptions (27%–48%) at MD and HD.
Necropsy findings: Cesarean-section data *[Implantation sites, pre- and postimplantation loss, etc.]*	MD and HD: Decreases in gravid uterine weight and fetal body weight HD: Decreases in the number of viable fetuses and litter size, increased postimplantation loss and increased total resorptions
Necropsy findings: Offspring	All doses caused a statistically significant increases in individual fetal skeletal variations, but total incidence of skeletal variations was statistically significant only at MD and HD. None of these changes were considered adverse since the variations are known to reverse during the postnatal development. LD: Increase in bent scapula and bent ribs; variations (additional ossification center neural arch cervical vertebrae, incompletely ossified bone in the skull), MD: Increase in bent humerus, bent radius, bent femur, bent scapula, a misshapen humerus; variations (incompletely ossified neural arch lumbar and thoracic vertebrae, bones in the skull), HD: increase in bent humerus, bent radius, bent ulna, bent femur and scapula; variations (incompletely ossified neural arch cervical and thoracic vertebrae, bones in the skull).

Abbreviations: BW, body weight; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose

13.1.1.6.4.2.2. Developmental Toxicity Study in Rabbits With Toxicokinetic Evaluation / RR 1002-500-044

Key Study Findings

- The NOAEL for maternal toxicity was 50 mg/kg/day (3.5 times the clinical dose at human dose of 180 mg, based on AUC), considering the decreased body weight gain and food consumption seen at 80 mg/kg/day.
- No adverse effect was observed on embryo-fetal development in all tested dose levels in rabbits. Hence, the NOAEL was established as the highest dose tested 80 mg/kg/day (12 times the clinical dose at human dose of 180 mg, based on AUC).
- The toxicokinetic evaluation confirmed in pregnant female rabbit systemic exposure to ETC-1002 and its metabolite ESP15228 during the dosing period.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 70. Methods of Oral Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 20, 50 and 80 mg/kg/day; Once daily; GD 6 to GD 18
Route of administration	Oral gavage
Formulation/vehicle	0.5% carboxymethylcellulose (sodium salt)
Species/strain	Time mated female rabbits/New Zealand White Hra:(NZW)SPF
Number/sex/group	23/sex/group
Satellite groups	TK: 4 time-mated females/Control group
Study design	Standard; Pregnant female rabbits were dosed from GD 6 to GD 18 and euthanized on GD 29.
Deviation from study protocol affecting interpretation of results	Deviations reported to not have affected the interpretation of the study findings.

Abbreviations: GD, gestation day; SPF, specific-pathogen-free; TK, toxicokinetics;

Table 71. Observations and Results of Oral Embryo-Fetal Developmental Study in Rabbits

Parameters	Major Findings
Mortality	Two deaths (control and MD): both considered not drug-related. MD: One female was found dead on GD 23. This animal did not have any abnormal clinical observations during the dosing period prior to death. The animal gained body weight; however, food consumption was remarkably decreased during the last recorded food consumption interval (GD 21-23) before it was found dead. At necropsy, the findings included an umbilical hernia with associated distended stomach and portions of the small intestine. As there were no mortalities at the higher dose level (80 mg/kg/day), this death was not considered test article-related, but rather the result of a congenital defect in this animal.
Clinical signs	HD: few/absent feces
Body weights	HD: Mean body weight change was statistically decreased during GD 6-10 and GD 6-19, with a body weight loss of 0.002 kg (compared to 0.040 kg gain in controls) and a decreased body weight gain of 0.105 kg (compared to 0.230 kg gain in controls), respectively. HD: Food consumption was also concomitantly decreased
Necropsy findings: Cesarean-section data	Unremarkable
Necropsy findings: Offspring	Unremarkable

Abbreviations: GD, gestation day; HD, high dose; MD, mid dose

13.1.1.6.4.3. Toxic Effects on Pre-and Postnatal Development, Including Maternal Function in Rats/RR 1002-500-042

Key Study Findings

- Bempedoic acid caused excessive maternal toxicities, including decreased activity, lower body weight, and high neonatal and maternal mortality during gestation and soon after birth in the 30 and 60 mg/kg/day dose groups. These groups were terminated early in lactation (LD 0-2).
- In the F0 generation, adverse maternal toxicities as evidenced by lower dam body weight and food consumption were observed throughout pregnancy and lactation at 20 mg/kg/day and transiently (lactation phase only) at 10 mg/kg/day. These coincided with increases in the occurrence of stillborn pup stillborn index at 10 and 20 mg/kg/day
- In the F1 generation, there were lower pup survival, lower body weight at 10 and 20 mg/kg/day. Slight delays in developmental landmarks (differences in learning and memory) and female sexual maturation (vaginal opening) were observed at 10 and 20 mg/kg/day.
- The maternal F_0 NOAEL was established as 5 mg/kg/day based on effect on body weight and adverse delivery data (increase in stillborn pups) at ≥10 mg/kg/day. These exposures approximate the human exposure at the 180 mg dose, based on AUC.
- The NOAEL for F1 pup growth, survival, and behavioral assessments was 5 mg/kg/day (below the clinical exposure at the human dose of 180 mg, based on AUC) due to lower viability index and delays in development (learning and memory) at ≥10 mg/kg/day).
- The NOAEL for the postweaning maturation and reproductive performance of the F1 generation were 20 mg/kg/day (11 times the clinical exposure at the human dose of 180 mg, based on AUC), considering the absence of significant drug-related effect on mating and fertility indices during postweaning phase.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 72. Methods of Pre-and Postnatal Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 5, 10, 20, 30, and 60 mg/kg/day once daily; GD 6 to LD 20
Route of administration	Oral gavage
Formulation/vehicle	0.5% carboxymethylcellulose (sodium salt)
Species/strain	Time mated female rats/ Wistar Han (b) (4) rats
Number/sex/group	25/sex/group
Satellite groups	None
Study design	Standard; Time mated pregnant female (F0 generation) were administrated orally once daily from GD 6 through LD 20. The mated females could give birth naturally. Litters were culled to 8/sex on LD4. Dams were euthanized on LD21.
Deviation from study protocol affecting interpretation of results	Deviations reported to not have affected the interpretation of the study findings.

Abbreviations: GD, gestation day; LD, lactation day

Table 73. Observations and Results, Pre- and Postnatal Study in Rats, F0 Generation-Dams

Parameters	Major Findings
Mortality	MD and HD: A total of 13 and 6 dams at MD and HD lost their pups between lactation day 0-1 and were euthanized. In addition, one dam at MD and two dams at HD were euthanized in extremis due to maternal toxicity, and two dams at HD were found dead on GD 20 and 21. Due to this, the MD and HD group were terminated early. Two additional treatment groups (5 and 20 mg/kg/day) and one additional control group were added to the study.
Clinical signs	HD: Decreased activity (also at MD), impaired righting reflex, few/absent feces, hunched posture, thin appearance and discolored skin.
Body weights	ID/MD/HD: Adverse maternal body weight loss (6%–23%) with concomitant food consumption (22%–70%) were observed during gestation phase; LD2, ID: Decreases in mean body weight up to 5 and 8% were noted during lactation phase. The changes at ID is considered adverse due to with parallel (s.s.) lowering of food consumption (up to 34%) at ID
Natural delivery and litter observations	LD1/LD2: No effect MD/HD: Mean gestation length were increases; 22.0 and 22.5 days, respectively versus 21.6 days in concurrent controls; s.s. LD2/ID/MD/HD: Percentage of pregnant females with stillborn pups, mean stillborn/litter and stillborn index were numerically increased as compared to the concurrent control and considered drug-related despite the changes were s.s. for still born/litter at MD. ID/MD/HD: Mean number of live born pups per litter were decreased numerically and were s.s. at ID and HD. MD/HD: Gestation index were decreased in dams treated at 30 mg/kg/day (n.s.s.) and 60 mg/kg/day (s.s.)

*Dams at 30 and 60 mg/kg/day were not available for evaluation due to lactation period due to early termination (LD 0-2) related to excessive toxicity. s.s. statistically significant, n.s.s not statistically significant,
Abbreviations: GD, gestation day; HD: 60 mg/kg/day; LD1, 5 mg/kg/day; LD2: 10 mg/kg/day; ID: 20 mg/kg/day; MD: 30 mg/kg/day; s.s., statistically significant; n.s.s., not statistically significant; PND, postnatal day

Table 74. Observations and Results, Pre- and Postnatal Study in Rats, F1 Generation

Parameters	Major Findings
Mortality	LD1: Unremarkable LD2/ID: lower s.s. mean viability indices (birth to lactation day 4 precull); 86 and 58% as compared to the control (>95%), Lactation index (postcull to lactation day 21) was comparable; 100% and 99% as compared to the control (>97%)
Clinical signs	LD1/LD2: decreased activity ID: Decreased activity, skin cold to touch (entire body) and gray discolored skin
Body weights	LD1: Unremarkable LD2/ID: In the ID, mean F1 pup body weights, were statistically lower at birth (about 14% lower), throughout lactation (12% to 26% lower), at weaning (about 10% lower), and on PND 28 (about 9% lower) in comparison to concurrent controls. At LD2, mean F1 pup body weights were statistically lower on lactation day 4 preculling (7% and 6% lower in males and combined sexes, respectively), LD 4 postculling (10% lower in males), and on LD 7 (8% and 7% lower in males and combined sexes) in comparison to concurrent controls.
Behavioral, sensory, and developmental evaluations	LD1: Unremarkable LD2: Attainment of air drop righting reflex was also prolonged in pups; however, this finding is not considered drug-related due to the absence of dose-relation. ID: The mean age in achieving of eye opening was statistically increased as compared to concurrent controls. The slight delay in eye opening correlated with decreased pup growth at this dose.
Motor activity and learning and memory	LD1: Unremarkable LD2: A lower percentage of males (passive = 66.7%; nonpassive = 33.3%) and females (passive = 68%; nonpassive = 32%) at 10 mg/kg/day exhibited an appropriate learned passive behavior as compared to the concurrent controls (passive = 88%–92%; nonpassive = 8%–12%). The female values were n.s.s., but considered drug-related the values were comparable to the controls ID: Fewer males were passive for two consecutive trials early in the testing period i.e., Trials 2 and 3 (23.8% in comparison to concurrent control (47.8%) and was s.s.; which was interpreted as slower learning of the task and considered test article-related.
Sexual maturation	ID: Days to completion of vaginal opening were statistically prolonged as compared to the concurrent controls, body weight at vaginal opening were comparable to control.
Reproductive performance [mating, fertility and fecundity indices, etc.]	Unremarkable
Uterine parameters	Unremarkable

Abbreviations: GD, gestation day; HD: 60 mg/kg/day; LD1, 5 mg/kg/day; LD2: 10 mg/kg/day; ID: 20 mg/kg/day; MD: 30 mg/kg/day; s.s., statistically significant; n.s.s., not statistically significant

13.1.1.6.4.4. Oral Juvenile Toxicity Study With a 6-Week Recovery Phase / RR 1002-500-055

Key Study Findings

- Bempedoic acid did not affect growth, neurobehavior (functional observational battery, startle response, motor activity, learning, and memory) and sexual maturation in juvenile rats treated up to 10 mg/kg/day.
- The NOAEL is established as 10 mg/kg/day (at doses resulting in exposures below the clinical exposure, based on AUC) considering the absence of effect on growth and neurobehavior in juvenile rats treated at the high dose (10 mg/kg/day) tested. However, the absence of a safety margin is not of clinical concern, because the toxicological profile of bempedoic acid in juvenile rats was comparable to that observed in adult rats. Findings observed in juvenile rats were related to rodent-specific PPARα effects (increase in liver weight and hepatocellular hypertrophy), which are not considered relevant to humans.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 75. Methods of Pre-and Postnatal Study in Rats

Parameters	Method Details
Dose and frequency of dosing	0 (vehicle), 1, 3, and 10 mg/kg/day, once daily for 11 weeks
Route of administration	Oral gavage
Formulation/vehicle	0.5% carboxymethylcellulose (sodium salt)
Species/strain	Rat: Wistar Han (b) (4)
Number/sex/group	Main and recovery group;15/sex/group
Satellite groups	TK: 9-32 sex/group
Study design	Juvenile rats were orally dosed with bempedoic acid for 11 weeks from PND 15 to PND 90
Deviation from study protocol affecting interpretation of results	Deviations reported to not have affected the interpretation of the study findings

Abbreviations: PND, postnatal day; TK, toxicokinetics

Table 76. Observations and Results

Parameters	Major Findings
Mortality	None
Clinical signs	None
Body weights	Unremarkable
Hematology	HD: minimal (4%–9%) reversible decreases in red blood cell mass (Hgb, Hct, MCH) with concurrent mild decreases in reticulocytes (17%).
Clinical chemistry	HD: Mild reversible increases in total protein (9%), albumin (8%), globulin (10%), and secondary increases in calcium (5%) were predominantly noted in females. Moreover, mild reversible increases in cholesterol (~81%) were observed in females at 10 mg/kg/day. This is consistent with compensatory increases in cholesterol observed in rodents following treatment with lipid-lowering drugs.
Histology	Consistent with earlier findings in adult rats, test article-related microscopic findings were present in the liver of females at 10 mg/kg/day; included minimal panlobular hepatocellular hypertrophy and minimal to mild increased hepatocellular eosinophilia
Neurodevelopment [FOB]	Unremarkable
Sextual maturation	Unremarkable

Abbreviations: FOB, Functional observational battery; Hct, hematocrit; HD, high dose; Hgb, hemoglobin; MCH, mean cell hemoglobin

13.1.1.6.5. Other Toxicology/Specialized Studies

13.1.1.6.5.1. Exploratory Mechanism of Toxicity Studies (RR 1002-500-025, RR 1002-500-026, RR 1002-500-027, RR 1002-500-030)

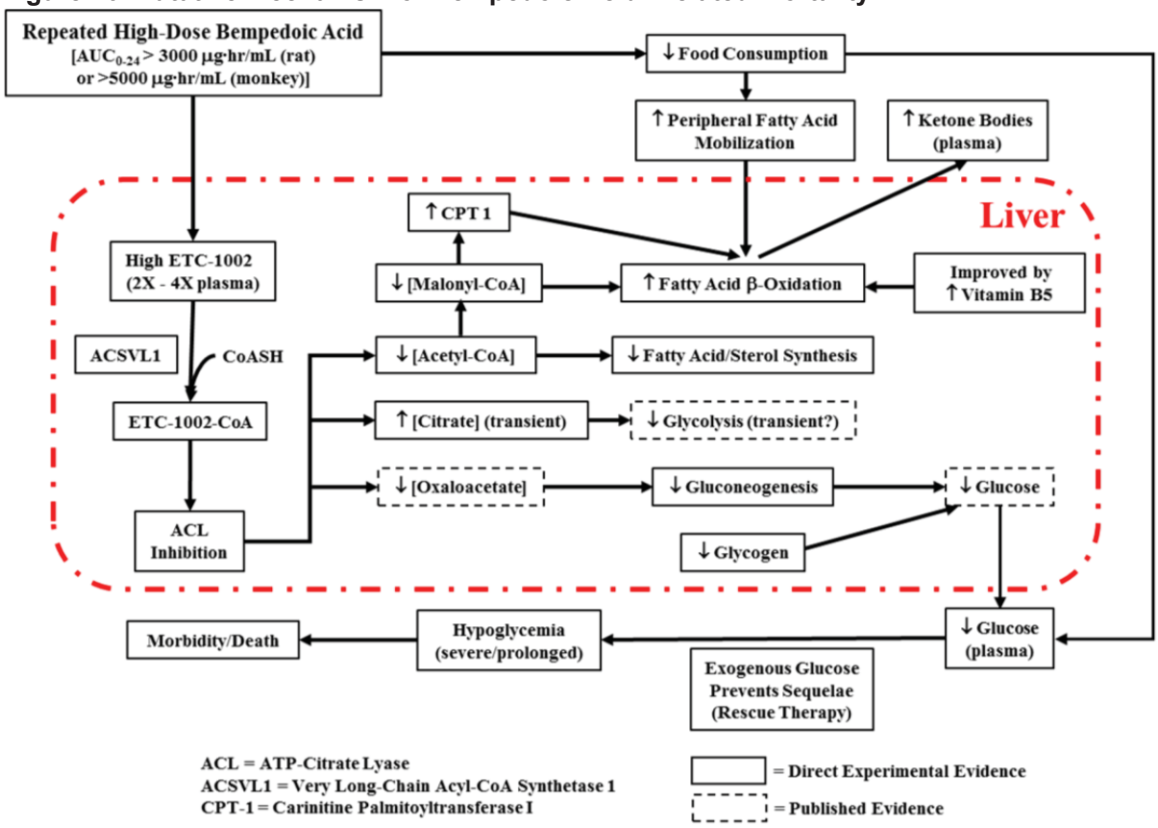
Administration of bempedoic acid at doses that produce high multiples of human exposure (>17 times the clinical exposure at the human dose of 180 mg, based on AUC) resulted in deaths in rats and monkeys in repeat-dose studies within the first 2 weeks treatment. In order to address the cause(s) of death, exploratory mechanistic rat and monkey studies were conducted. In one study, male Wistar rats were given vehicle or 300 mg/kg/day bempedoic acid. Administration of bempedoic acid was discontinued on Day 5 when mortality in this group was approximately 25%, a predefined criterion for studying reversibility of toxic effects in survivors. Clinical pathology parameters (assessed by sequential sampling on Day 1, 2,4, 8, 12, and 24 hours) showed severely reduced blood glucose (hypoglycemia), increases in free fatty acids (FFA), lactic acid, and anion gap within 8 hours of treatment with high dose (300 mg/kg) of bempedoic acid in rats. These changes were accompanied with severe clinical signs (hunched posture, decreased activity, tremor, body weight loss and decreased feeding). Marked hypoglycemia and associated clinical symptoms without lactic acidosis were also noted in monkeys dosed with 200 mg/kg of bempedoic acid in an exploratory study, suggesting a common mechanism leading to toxicity in both species.

Another study was conducted in rats to test the hypothesis that the high-dose bempedoic acid–dependent increases in plasma FFA and decreases in glucose are suggestive of altered fatty acid metabolism that may lead to changes in energy production and substrate. Groups of male rats were given vehicle or bempedoic acid at 100 and 300 mg/kg/day by oral gavage for 3 days. Blood and liver samples were analyzed for changes in parameters indicative of effect on glycolysis (i.e., glucose, lactate, and pyruvate) and fatty acid oxidation (e.g., acylcarnitines). Acylcarnitines are products of transacylation of acyl-CoA with carnitine, and relative changes (versus control) are indicators of effects on mitochondrial energy metabolism. In the liver, bempedoic acid treatment increased the sum of 16-carbon to 6-carbon aliphatic acylcarnitines (summed C16-C6) and the ratio of C16 to C4 (C16:C4 ratio), which are measures of the metabolism of 16-carbon aliphatic acyl-CoA. Both indicators were increased by up to 61% and 4-fold, respectively. The changes in the concentrations of acylcarnitines are suggestive of decreased mitochondrial β-oxidation of 16-carbon aliphatic acyl-CoA (palmitoyl-CoA).

In general, the completed exploratory studies suggest that a sustained high systemic exposure to bempedoic acid (e.g., at doses resulting in exposures >17 times the clinical exposure at 180 mg/day, based on AUC) leads to reduced fatty acid and mitochondrial β-oxidation (and increases in plasma FFA). The severe toxicity observed in rats and monkeys can thus be explained by a significant reduction in fatty acid mitochondrial β-oxidation (a significant substrate for energy production coupled with a dramatic increase in the utilization of glucose). Increased glycolysis and reduced food intake would thus lead to glycogen depletion and exaggerated hypoglycemia in the animals. Animals with reduced food consumption (e.g., rats) progress to acidosis in this scenario. In addition, the absence of oxaloacetate (precursor required for gluconeogenesis) due to inhibition of ACL by bempedoic acid might lead to reduction in glucose synthesis, further compounding this effect (Figure 20).

In both rat and monkey studies, discontinuation of dosing resulted in 100% survival. Based on these findings, both hypoglycemia and metabolic acidosis were monitored in the clinical program.

Figure 20. Putative Mechanism of Bempedoic Acid–Related Mortality



Source: Excerpted from the Applicant's submission

13.1.1.6.5.2. Combination Repeat-Dose Toxicity Studies With Bempedoic Acid and Statins (Atorvastatin) in Monkeys (RR-1002-500-060, RR-RR 1002-500-060, RR 1002-500-065)

The potential for additive or synergistic toxicologic interaction between bempedoic acid and atorvastatin (a potent statin) was studied, owing to their overlapping mechanisms of action, common target organs, and the very high likelihood of concomitant administration for hypercholesterolemia. Short-term (2-week) and pivotal subchronic (3-month) studies were conducted in monkeys. In the initial combination monkey study, unexpected excessive toxicities including deaths and/or moribund sacrifices occurred in 14 out of 30 animals between Day 6 and 13 upon coadministration of ≥10 mg/kg/day doses of bempedoic acid (resulting in exposures that approximate the human exposure at the 180 mg dose, based on AUC) coadministered with 40 mg/kg/day atorvastatin (resulting in exposures 10-fold the human exposure maximum recommended human dose (MRHD) of 80 mg), based on body surface area (mg/m^2).

In addition, severe clinical signs (decreased activity, hunched posture, thin/unkempt appearance), hypoglycemia, and degenerative liver (midzonal hepatocytes necrosis with correlative increases in LFTs) and kidney toxicities were observed. As a consequence, dosing was discontinued on Day 13 of the planned 90-day study. In a subsequent 2-week dose-range–finding study in monkeys, morbidity occurred in monkeys administered 30 mg/kg/day of bempedoic aid (7-fold MRHD) and coadministered 20 mg/kg/day atorvastatin. In addition, hypoglycemia and adverse liver toxicity was observed for the combination of bempedoic acid (7-fold MRHD) with atorvastatin at ≥10 mg/kg/day (2.5-fold MRHD). The definitive 90-day combination toxicity study was conducted using lower doses of atorvastatin, which approximate the clinical dose 80 mg/day. Synergistic toxicologic interactions were not present in monkey given up to 20 mg/kg/day (3-fold MRHD) of bempedoic acid with exposure to atorvastatin at doses resulting in clinical exposures of atorvastatin.

13.1.1.6.5.3. 13-Week Oral Gavage Toxicity Study in CD-1 Mice/RR 1002-500-029

A dose-range–finding toxicity study was conducted to support the dose selection for the 2-year mouse carcinogenicity study. CD-1 mice (10/sex/group) were administered vehicle (0.5% carboxymethylcellulose or bempedoic acid at 100, 300, and 1,000 mg/kg/day. Bempedoic acid caused deaths in three females treated at 1,000 mg/kg/day between Day 27 and 59. Premonitory clinical signs in these moribund animals include hunched posture, distended abdomen, tremors, decreased activity, and unkempt appearance. Contrary to the finding in other species, body weight was unaffected in males, while in females, body weight was increased (7% to 10%) and correlated with 9% to 57% increase in food consumption at 1,000 mg/kg/day.

Red blood cell mass, the liver, and the male reproductive organs were target organs of toxicity in mice. Decreases (6% to 12%) in red blood cell mass including, erythrocytes, Hgb, Hct, mean cell Hgb and 10% increases in mean corpuscular volume were observed in both sexes predominantly at 1,000 mg/kg/day. Bempedoic acid–related increases in ALP (1.3- to 3-fold), AST (1.4 to 12-fold) and TB (~2-fold) were noted at ≥300 mg/kg/day. Liver transaminase increases correlated with adverse histologic changes in the liver at all doses included minimal to moderate hepatocellular degeneration, minimal to severe hepatocellular cytoplasmic alteration, minimal to moderate diffuse vacuolation, and increased Kupffer cell pigment. Individual hepatocyte necrosis was observed in males and females at ≥300 mg/kg/day. Consistent with PPARα activity of bempedoic acid, liver enlargements (49% to 143%) and centrilobular and panlobular hepatocellular hypertrophy were observed in both sexes at all doses. This is further supported by ultrastructural changes—increased peroxisomes noted at 100 mg/kg/day, the only dose level evaluated. Bilateral seminiferous tubule degeneration/atrophy was noted in one male at 300 mg/kg/day and three males at 1,000 mg/kg/day. Secretory depletion in seminal vesicles and increased germ cell debris in epididymides were noted in two males at 1,000 mg/kg/day. Dose-related 6% to 38% decreases in absolute and relative seminal vesicle and testes weights were observed in males at ≥100 mg/kg/day. Due to adverse toxicities reported in the liver, a NOAEL dose was not identified in this study for both sexes.

13.1.1.6.5.4. 13-Week Oral Toxicity Study Followed by 4-Week Recovery Period in Wistar Rats/RR 1002-500-013

A subchronic 13-week study was conducted with daily oral gavage treatment with bempedoic acid in Wistar rats (15/sex/group) at dose levels of 3, 10, 30, and 60 mg/kg/day. The study also included a 4-week recovery period and additional parameters to evaluate potential PPAR effects. In general, the toxicity findings in this study were consistent with the pivotal study and included reduced body weight gains (11% to 26%) and transient lowered food consumption in animals treated at ≥30 mg/kg/day. Decreases in RBC mass and changes in renal parameters (increase in creatinine) were also observed. The liver, kidney, and spleen were target organs of toxicity. Liver and splenic enlargements were reported in all treated animals and in high-dose males, respectively. Changes indicative of PPAR activity including liver centrilobular hepatocellular hypertrophy, induction of activities and/or mRNA levels of peroxisomal enzymes (Cyp4A1, ACOX1 and PDK4), and increase in the number of peroxisomes were notable.

The liver also had single cell necrosis of the hepatocytes, focal ductal hyperplasia at ≥30 mg/kg/day with hepatocellular vacuolation, and a higher severity of Oil Red O staining (lipid accumulation) in males at 60 mg/kg/day. In the spleen, increases in the severity of splenic extramedullary hematopoiesis at all doses and capsular fibrosis were observed at ≥30 mg/kg/day. Similar spleen changes were absent in the pivotal chronic rat study. Increases in the severity of renal tubule dilatation was reported in animals treated at ≥10 mg/kg/day as compared to the control. The majority of the findings were reversible except the hepatocellular hypertrophy, focal ductal hyperplasia, and hepatocellular vacuolation findings were still apparent in some recovery animas treated at ≥10 mg/kg/day. Therefore, the NOAEL was established as 3 mg/kg/day (below the clinical exposure at 180 mg, based on AUC).

13.1.1.6.5.5. 13-Week Oral Toxicity Study Followed by a 4-Week Recovery Period in Cynomolgus Monkeys/RR 1002-500-014

In this study, groups of cynomolgus monkeys (5/sex/group) were given bempedoic acid orally at 3, 10, 30, and 60 mg/kg/day. Four monkeys treated at 60 mg/kg/day (> MTD) were euthanized on Days 11, 14, and 71 due to poor and deteriorating condition (decreased activity, appetite, prostration, body weight loss, no food consumption, and dehydration) prior to the end of the study. The primary target tissues and organs were RBC mass, liver, kidney, and bone marrow. A statistically significant reduction (11% to 15%) in red cell mass (RBC, Hgb, Hct) were noted at ≥30 mg/kg/day. Plasma creatinine levels were increased 41% in males at 60 mg/kg/day and 46% to 51% in females at ≥30 mg/kg/day in the absence of kidney histology changes at all tested doses. In addition, decreases in glucose were observed at all dose levels and considered as the cause of death in monkeys treated at 60 mg/kg/day.

Consistent with the pharmacology of bempedoic acid, lower cholesterol levels were noted at 60 mg/kg/day. Increases in absolute (28% to 74%) and relative (34% to 72%) liver weight with correlative hepatocellular hypertrophy were seen at all doses. Periportal hepatocellular vacuolation with increased intensity of Oil Red O staining (lipids) were present at ≥30 mg/kg/day.

Drug-related changes in the bone marrow include reticuloendothelial hyperplasia, and mild granulocytic hyperplasia. Mild to moderate changes (increased spindle cells, pinkish matrices) indicative of early myelofibrosis were noted at 60 mg/kg/day dose. Of note, neither changes in RBC mass nor cytotoxicity in bone marrow was apparent in monkeys treated long term (i.e., 9 months at doses up to 60 mg/kg/day) with bempedoic acid.

The association between reduction in RBC and direct toxicity on the bone marrow is not clearly established for bempedoic acid because bone marrow change is not consistently observed in animals with lower RBC parameters except in this single study. Bempedoic acid modestly induced the activity of hepatic peroxisomal enzymes (CYP4A1, ACOX) at ≥10 mg/kg/day and increased liver peroxisomal numbers at 30 mg/kg/day (only dose tested). However, no PPAR-related changes were seen in the heart and skeletal muscle. The NOAEL in monkeys was established as 10 mg/kg/day (1.3-fold MRHD), based on the adverse changes in RBC and creatinine parameters at doses ≥30 mg/kg/day.

Impurities

The Applicant identified three compounds: (b) (4) structural alerts in the synthesis of bempedoic acid. The mutagenicity potential of (b) (4) were evaluated in Ames assays in the presence and absence of metabolic activation (b) (4) were negative in the Ames assay (b) (4) was not evaluated in a bacterial mutagenicity assay, because (b) (4) is considered nonmutagenic (class 4) as per ICH M7. All the three impurities are controlled as nonmutagenic (b) (4) per ICH Q3A. All other impurities were below the limits requiring qualification per ICH Q3A and ICH Q3B.

Referenced NDAs, BLAs, DMFs

Not applicable.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

14.1.1. Plasma Protein Binding (Studies RR 1002-500-009, RR 1002-500-058)

In human plasma, binding of ETC-1002 at concentrations of 3 to 100 µg/mL to plasma proteins was linear: the percent bound remained relatively constant (97.4% to 95.4%). At 300 µg/mL, binding to human plasma proteins decreased slightly to 91.6%.

14.1.2. Blood-to-Plasma Partitioning

No in vitro blood-to-plasma partitioning study was conducted. However, based on results from a radio-labeled mass balance study (Study 1002-011) in healthy volunteers, geometric mean whole blood to plasma total radioactivity concentration ratios ranged from 0.518 to 0.572. The whole blood to plasma ratios for C_{max} and $AUC_{(0\text{-}inf)}$ were 0.489 and 0.498. The radioactivity was accounted by bempedoic acid (ETC-1002), the primary metabolite, ESP15228, and other glucuronidation metabolites. Therefore, very limited bempedoic acid and its metabolites are distributed into red blood cells.

14.1.3. In Vitro Metabolism (Studies RR 1002-500-010, RR 1002-500-045, RR 1002-500-046)

Bempedoic acid underwent similar metabolic pathways in freshly isolated cultured rat, mouse, monkey, and human hepatocytes. The major routes of metabolism in all species were via direct acyl glucuronidation and glycerol conjugation. No human-specific metabolites were identified.

ETC-1002 and ESP15228 were incubated in pooled microsomes from 50 donor human livers in the presence and absence of NADPH at concentrations of 0.344 and 20.5 µg/mL [^{14}C]-ETC-1002 acid and 0.342 and 2.74µM [^{14}C]-ESP15228. In the presence of NADPH, metabolism of both ETC-1002 and ESP15228 was minimal. After incubation for 60 minutes, approximately 1% of [^{14}C]-ETC-1002 was converted to [^{14}C]-ESP15228, whereas approximately 5% of [^{14}C]-ESP15228 was converted to [^{14}C]-ETC-1002. The conversion of ETC-1002 to ESP15228 and vice versa observed in human hepatic microsomal incubations supplemented with NADPH is likely mediated by an aldo-keto reductase, but not CYP isozymes.

Glucuronidation of [^{14}C]-ETC-1002 (0.344 and 20.5 µg/mL) and [^{14}C]-ESP15228 (0.342 and 2.74 µg/mL) was assessed in human liver microsomes in the presence of UDPGA. Individual (cDNA) expressed UGT isozymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15) were assessed. Overall, 2.04% of [^{14}C]-ETC-1002 and 6.30% of [^{14}C]-ESP15228 formed glucuronide. [^{14}C]-ETC-1002-glucuronide was only observed after incubation with UGT2B7, accounting for up to 2.40% of the total radioactivity. [^{14}C]-ESP15228-glucuronide was also only observed after incubation with UGT2B7, accounting for up to 7.66% of the total radioactivity.

14.1.4. Inhibition of CYP Isozymes (Study RR 1002-500-011)

Direct inhibition: ETC-1002 concentrations up to 103 µg/mL did not significantly inhibit (>50%) CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 (1OHMDZ and 6ßT).

Time-dependent inhibition: Following a 30-minute pre-incubation in the presence and absence of NADPH, ETC-1002 showed no significant changes (>2-fold) in IC_{50} values for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 (1OHMDZ and 6ßT). This lack of significant change indicates that bempedoic acid is not likely a time-dependent (mechanism-based) inhibitor of these isoforms.

14.1.5. Induction Potential of P450 (Study RR 1002-500-012)

Bempedoic acid did not significantly induce CYP1A2 or CYP2B6. ETC-1002 induced CYP2C8, CYP2C9, CYP2C19, and CYP3A4 (6ßT) enzyme activity at the highest concentration (103 µg/mL) but not at the lower concentrations (1.0 and 10.3 µg/mL). These increases were not uniformly observed across hepatocyte donors except with CYP2C8. It is highly unlikely that bempedoic acid would induce CYP2C8, CYP2C9, CYP2C19, or CYP3A4 in vivo, as human efficacious steady state exposure (20.0 µg/mL) is less than 20% of the concentration of ETC-1002 that demonstrated induction (103 µg/mL).

14.1.6. Inhibition Potential of UGTs (Study RR 1002-500-058)

The inhibition of UGT activity in hrUGTs by 200 µg/mL (582µM) ETC-1002 was 62.5%, 52.5%, 28.1%, 33.2%, 40.7%, and 27.7% for UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, and UGT2B15, respectively. The inhibition of UGT activity in hrUGTs by 70 µg/mL (116µM) ETC-1002-glucuronide was 54.4%, 30.5%, 44.8%, 25.6%, 35.3%, and 35.2% for UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, and UGT2B15, respectively. Therefore, it appears that there is a low potential for a significant clinical drug-drug interaction mediated by UGT1A1 and UGT1A3 inhibition.

14.1.7. Drug Transporters (Studies RR 1002-500-033, RR 1002-500-056, RR 1002-500-071, RR 1002-500-073)

ETC-1002 at a concentration of 15 µg/mL was not significantly transported by P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), OAT1, OAT3, OATP1B1, or OATP1B3. ESP15228 at a concentration of 6 µg/mL was not significantly transported by P-gp, BCRP, OAT1, OAT1B1, or OATP1B3. Initial study indicated transport by OAT3 at 6 µg/mL. The cellular accumulation of ESP15228 in cells transfected with OAT3 was statistically different

from the corresponding control cells, and the difference was abolished in the presence of OAT3 inhibitor. However, upon repeat analysis including additional test concentrations ESP15228 uptake was not OAT3-dependent. There were no statistically significant differences between cells transfected with OAT3 and the corresponding control cells in any of the concentrations tested.

ETC-1002 did not appear to be a substrate of OAT1, OAT3, OCT2, OAT1B1, OATP1B3, BCRP, or P-gp. ETC-1002-glucuronide was not a substrate for OAT1, OCT2, OAT1B1, or OATP1B, but appeared to be a substrate for OAT3. ETC-1002-glucuronide may be a substrate for BCRP and P-gp, although results were inconsistent between models.

Bempedoic acid does not appear to be a clinically relevant substrate for human OAT2, OCT1, MATE1, MATE2-K, or BSEP under the study conditions. Bempedoic acid was evaluated at 58μM (20 μg/mL), 290μM (100 μg/mL), and 580μM (200 μg/mL) concentrations, or 1 times, 5 times, and 10 times total C_{max}. At all concentrations of bempedoic acid tested, less than 2-fold difference of uptake was observed in transporter-transfected cells compared to control cells for OAT2, OCT1, MATE1, MATE2-K, and BSEP.

ETC-1002-glucuronide was not actively transported and does not appear to be a clinically relevant substrate for human OAT2, OCT1, MATE1, MATE2-K, or BSEP under the study conditions. At all concentrations of ETC-1002-glucuronide tested, <2-fold difference of uptake was observed in transporter-transfected cells compared with control cells for OAT2, OCT1, MATE1, MATE2-K, and BSEP. Incubation of 146.9μM (76.5 μg/mL) or 10 times total C_{max} of ETC-1002-glucuronide in the presence of prototypical reference inhibitors for each transporter did not alter the uptake (<2-fold).

14.1.8. Inhibition Potential of Transporters (Studies RR 1002-500-034, RR 1002-500-057, RR 1002-500-070, RR 1002-500-072)

ETC-1002 at a concentration of 10 μg/mL did not significantly inhibit OCT2, OAT1, OAT3, OATP1B1, OATP1B3, P-gp, or BCRP-mediated transport. ESP15228 at 3 μg/mL decreased the BCRP transport with a small, statistically significant inhibition of 10.6%.

ETC-1002 and ETC-1002-glucuronide did not inhibit OAT1, OCT2, BCRP, or P-gp. ETC-1002 demonstrated weak inhibition of OATP1B1 (32% to 74%) and OATP1B3 (18% to 62%) at 20 μg/mL and 200 μg/mL concentrations, which are approximately equal to 1 times and 10 times the observed human steady-state ETC-1002 C_{max} based on total concentration. Lower levels of inhibition were reported at the lowest doses tested; these were statistically significant but not considered clinically relevant. ETC-1002-glucuronide demonstrated weak inhibition of OATP1B1 (27% to 69%) and OATP1B3 (20% to 74%) at 10 μg/mL and 70 μg/mL concentrations, which are approximately equal to 1 and 10 times the observed human steady-state ETC-1002-glucuronide C_{max} based on total concentration. ETC-1002 also inhibited OAT3 (48.2%) at a concentration of 40 μg/mL. BCRP was not appreciably inhibited in vitro by either bempedoic acid at concentrations up to 200 μg/mL (14% inhibition) or by ETC-1002-glucuronide at concentrations up to 70 μg/mL (24% inhibition) making an effect on BCRP unlikely.

OAT2 was inhibited 96.0% by 580μM bempedoic acid (200 μg/mL, 10× total C_{max}, or 333× free C_{max}). In the concentration range of 1.74 to 580μM (0.6 to 200 μg/mL or 0.03× to 10× total C_{max} or 333× free C_{max}), bempedoic acid showed a maximum inhibition of 64.3%. The IC_{50} for OAT2 was 411μM (142 μg/mL or 7× total C_{max}). Bempedoic acid is very close to the solubility limit at 580μM, which may contribute to the variability in percent inhibition at this concentration between the two evaluations. OCT1 was inhibited 24.3% by 580μM bempedoic acid (200 μg/mL or 10× C_{max}, or 333× free C_{max}). For MATE1, no inhibition was observed at 580μM bempedoic acid (200 μg/mL, 10× C_{max}, or 333× free C_{max}), but a statistically significant 56.8% increase in probe substrate uptake was observed in the presence of bempedoic acid. For MATE2-K, no inhibition was observed at 580μM bempedoic acid (200 μg/mL, 10× C_{max}, or 333× free C_{max}). Inhibition of BSEP was concentration dependent, with 10.3%, 19.1%, and 38.6% inhibition at 58μM (1× C_{max}), 174μM (3× C_{max}), and 580μM (10× C_{max} or 333× free C_{max}) bempedoic acid, respectively.

ETC-1002-glucuronide did not inhibit human OCT1-, MATE1-, and MATE2-K–mediated transport. Minimal inhibition was observed for OAT2 (16.6%), and BSEP (37.7%) at concentration that are 10× total C_{max} (unbound plus bound).

14.1.9. Effect on hERG Potassium Channel (Study RR 1002-500-007)

ETC-1002 inhibited hERG current by (mean ± SEM) 1.6±0.6% at 10μM (n=4), 2.3±0.9% at 100μM (n=3), 1.7±0.7% at 300μM (n=3), and 5.4±0.4% at 1,000μM (n=3) versus 0.2±0.7% (n=3) in control. HERG inhibition at 1,000μM was statistically significant ($p<0.05$) when compared with vehicle control values. The IC_{50} for the inhibitory effect of ETC-1002 on hERG potassium current was not calculated but was estimated to be >1,000μM. Under similar conditions, the positive control (60nM terfenadine) inhibited hERG potassium current by (mean ± SD) 80.6±2.2% (n=2).

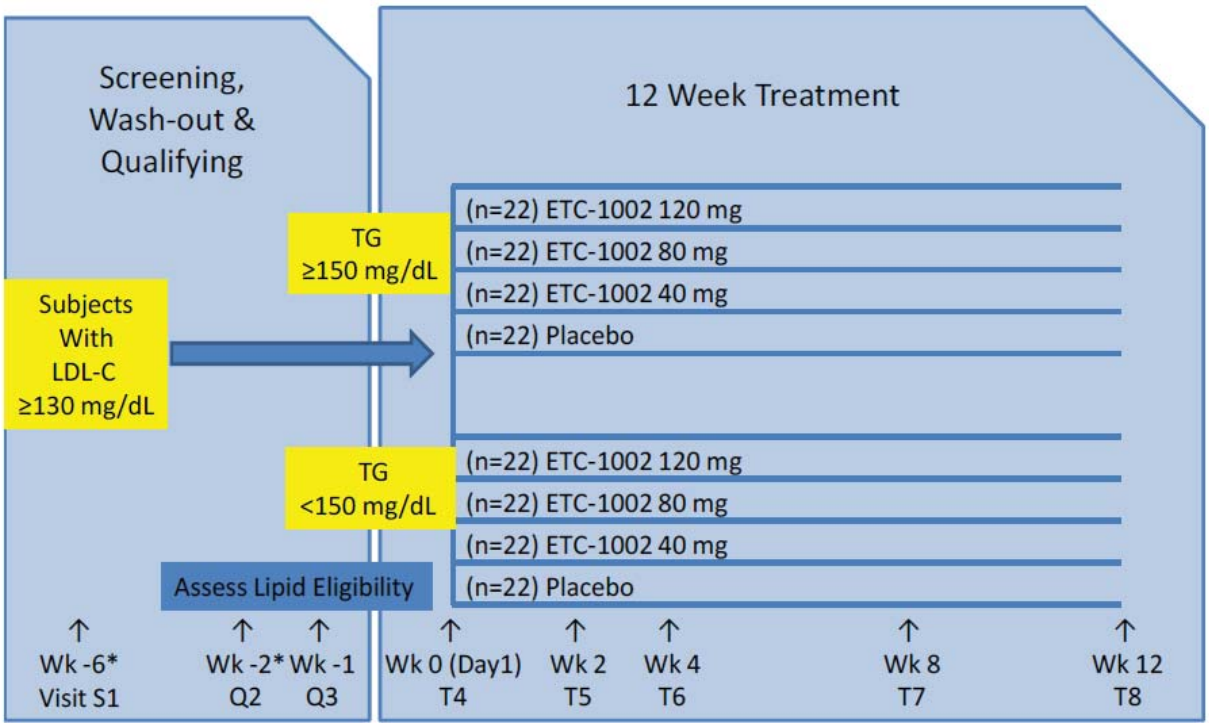
14.2. In Vivo Studies

14.2.1. Dose-Response Relationship

The dosing regimen selection of 180 mg QD was based on six phase 2 dose-ranging studies, including Studies 1002-003, 1002-005, 1002-006, 1002-1007, 1002-008, and 1002-009. Primarily, Studies 100-2003, 1002-008, and 1002-009 contributed to the dose-response evaluation. Studies 1002-005, 1002-006, 1002-007 adopted a forced titration design and were supportive for the dose-response evaluation.

Study 1002-003 was a multicenter, randomized, double-blind (subject, site, and sponsor), placebo-controlled, parallel group study. Subjects were stratified into a normal (<150 mg/dL) or elevated (≥150 mg/dL) TG stratum and randomized to receive with equal probability single daily doses of 40 mg, 80 mg, or 120 mg ETC-1002 or placebo for the 12-week period. The study design for 1002-003 is presented in Figure 21.

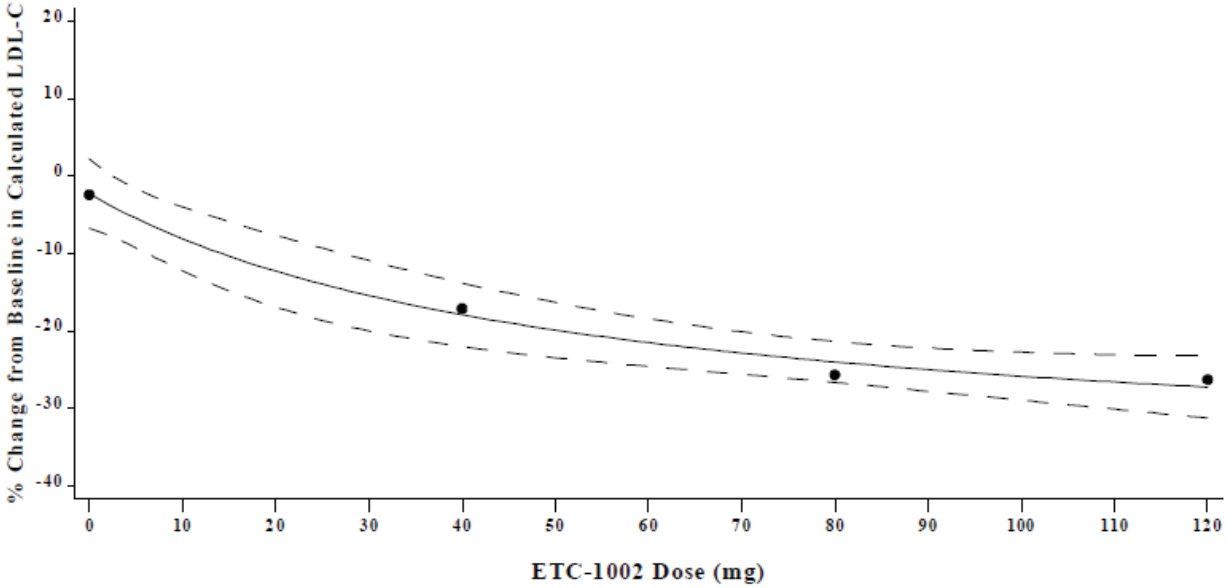
Figure 21. Design, Study 1002-003



Source: Figure 1 in Study 1002-003 CSR
* Visits can be combined if NOT washing-off of lipid-regulating medications
Abbreviations: LDL-C, low-density lipoprotein cholesterol; n, number of subjects in group; S, screen visit; T, treatment visit; TG, triglycerides

The dose-response curve showing the percent change from baseline to Week 12 in LDL-C (mg/dL) for the mITT population is shown in Figure 22; the data demonstrate the dose-related improvement for the primary efficacy measurement.

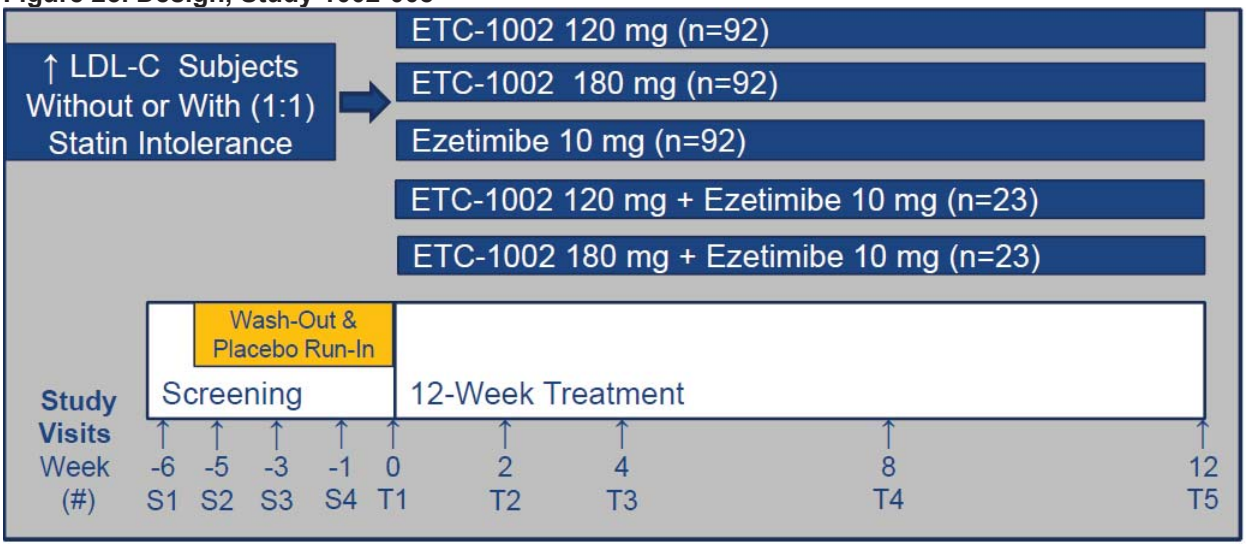
Figure 22. Dose-Response Relationship Between ETC-1002 and Percent Change From Baseline to Week 12 in Calculated LDL-C (mg/dL) mITT Population



Source: Figure 3 in Study 1002-003 CSR
Abbreviations: LDL-C, low-density lipoprotein cholesterol; mITT, modified intention-to-treat

Study 1002-008 was a randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of ETC-1002, ezetimibe, and the combination in hypercholesterolemic patients with or without statin intolerance. A total of 349 patients were stratified (1:1) by history of statin intolerance. At Week 0 (Visit T1), patients were randomized in a ratio of 4:4:4:1:1 to receive either ETC-1002 120 mg, ETC-1002 180 mg, ezetimibe 10 mg, ETC-1002 120 mg + ezetimibe 10 mg, or ETC-1002 180 mg + ezetimibe 10 mg once daily for 12 weeks (Figure 23).

Figure 23. Design, Study 1002-008



Source: Figure 1 in Study 1002-008 CSR
Abbreviations: LDL-C, low-density lipoprotein cholesterol; n, number of subjects in group; S, screen visit; T, treatment visit

The percent change from baseline in LDL-C for each treatment group are present in Table 77.

Table 77. Percent Change in LDL-C From Baseline to Week 12 Endpoint With Treatment Comparisons, mITT Population

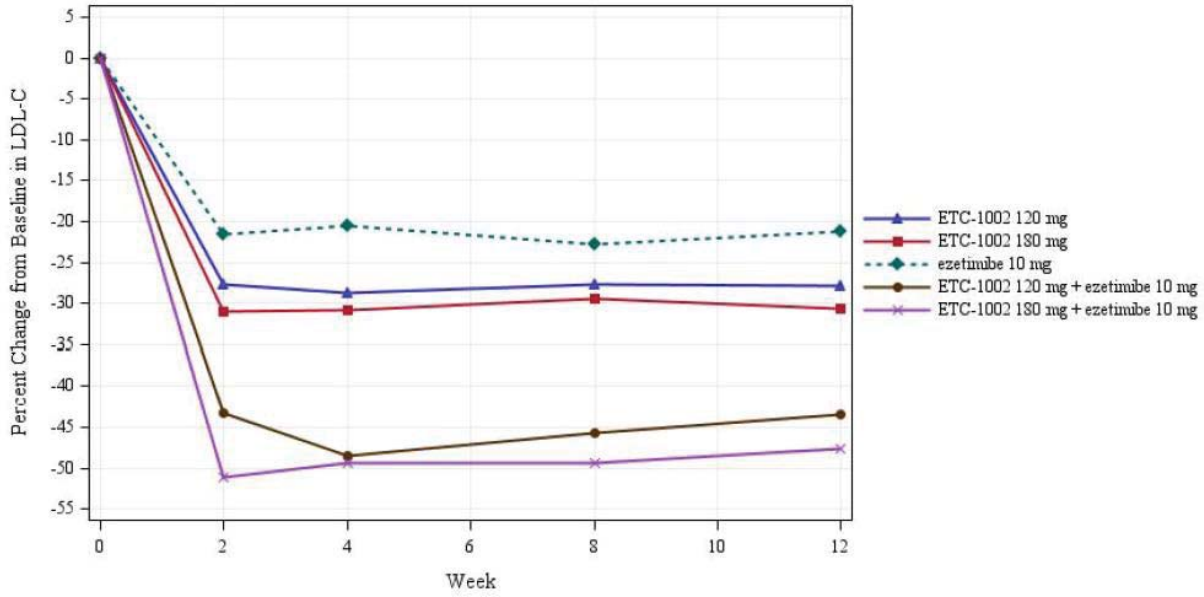
Treatment	n [1]	Baseline (mg/dL) [2] Mean (SD)	Week 12 endpoint (mg/dL) [3] Mean (SD)	Percent Change [4]	
				Mean (SD)	LS Mean (SE)
ETC-1002 120 mg	97	164.25 (27.75)	118.75 (29.51)	-27.42 (14.51)	-27.47 (1.316)
ETC-1002 180 mg	99	165.98 (23.58)	115.11 (25.20)	-30.25 (13.82)	-30.13 (1.303)
Ezetimibe 10 mg	98	165.00 (25.15)	129.18 (20.11)	-21.23 (9.36)	-21.22 (1.309)
ETC-1002 120 mg + ezetimibe 10 mg	24	161.13 (26.12)	91.63 (29.13)	-42.73 (18.58)	-43.08 (2.647)
ETC-1002 180 mg + ezetimibe 10 mg	22	163.86 (26.50)	85.55 (21.25)	-47.65 (11.06)	-47.70 (2.764)
ETC-1002 Pooled + ezetimibe 10 mg	46	162.43 (26.05)	88.72 (25.57)	-45.08 (15.48)	-45.39 (1.914)

Treatment Comparison	Difference [4]		
	LS Mean (SE)	95% CI	p-value
ETC-1002 120 mg vs. ezetimibe 10 mg	-6.25 (1.856)	(-9.90, -2.60)	0.0008
ETC-1002 180 mg vs. ezetimibe 10 mg	-8.91 (1.847)	(-12.54, -5.28)	<0.0001
ETC-1002 120 mg + ezetimibe 10 mg vs. ezetimibe 10 mg	-21.86 (2.953)	(-27.67, -16.05)	<0.0001
ETC-1002 180 mg + ezetimibe 10 mg vs. ezetimibe 10 mg	-26.48 (3.059)	(-32.50, -20.46)	<0.0001
ETC-1002 Pooled + ezetimibe 10 mg vs. ezetimibe 10 mg	-24.17 (2.319)	(-28.73, -19.61)	<0.0001
ETC-1002 180 mg vs. ETC-1002 120 mg	-2.66 (1.852)	(-6.30, 0.98)	0.1518

Source: Table 17 in 1002-008 CSR
[1] n is the number of patients with values at both baseline and Week 12 endpoint
[2] Baseline is the mean of the values from Weeks -1 and 0
[3] Week 12 endpoint is the last available post-baseline value
[4] Least-squares mean, SE, 95% CI, and 2-sided p-value are from an analysis of covariance model with terms for treatment and statin intolerance, and baseline value as a covariate
Abbreviations: CI, confidence interval; LS, least-squares; mITT, modified intent-to-treat; n, number of subjects in group; SD, standard deviation; SE, standard error

Figure 24 presents the mean percent change in LDL-C from baseline over time in the mITT population. All treatment groups demonstrated a reduction in LDL-C over time from baseline. Across treatment groups, reductions in LDL-C were apparent by Week 2 of treatment.

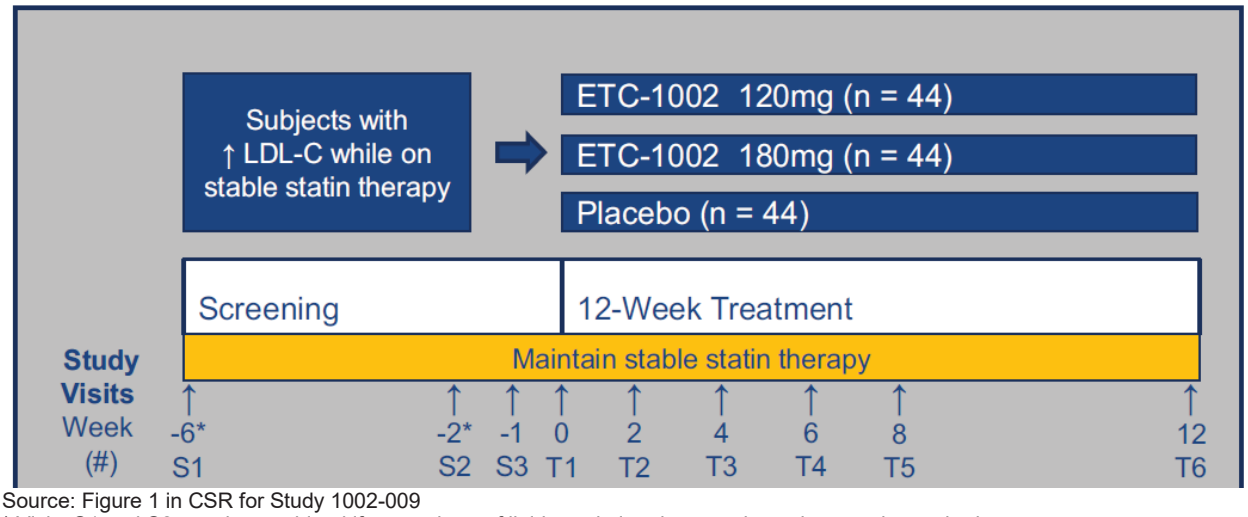
Figure 24. Percent Change From Baseline in LDL-C Over Time, mITT Population



Source: Figure 1 in Study 1002-008 CSR
Abbreviations: LDL-C, low-density lipoprotein cholesterol; mITT, modified intent-to-treat

Study 1002-009 was a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ETC-1002 versus placebo in patients with hypercholesterolemia receiving ongoing statin therapy. Approximately 132 patients were planned to be randomized in a 1:1:1 ratio on Day 1 (Week 0, Visit T1) to receive either ETC-1002 120 mg, ETC-1002 180 mg, or placebo for 12 weeks (Figure 25).

Figure 25. Design, Study 1002-009



Source: Figure 1 in CSR for Study 1002-009
* Visits S1 and S2 may be combined if no washout of lipid-regulating drugs and supplements is required
Abbreviations: LDL-C, low-density lipoprotein cholesterol; n, number of subjects in group; S, screen visit; T, treatment visit

The percent change from baseline in LDL-C for each treatment group are presented in Table 78.

Table 78. Percent Change in Low-Density Lipoprotein Cholesterol From Baseline to Week 12 Endpoint With Treatment Comparisons, mITT Population

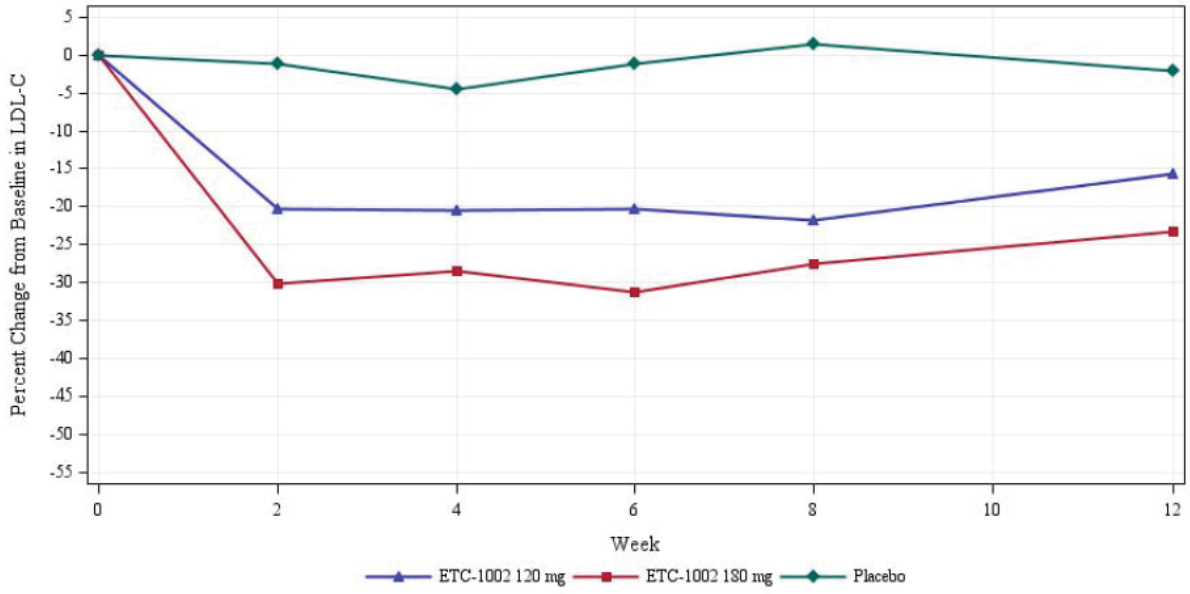
Treatment	n [1]	Baseline (mg/dL) [2] Mean (SD)	Week 12 Endpoint (mg/dL) [3] Mean (SD)	Percent Change [4]	
				Mean (SD)	LS Mean (SE)
Placebo	43	131.9 (21.78)	127.8 (31.13)	-2.0 (23.20)	-4.2 (4.19)
ETC-1002 120 mg	41	134.0 (19.86)	111.9 (26.84)	-15.9 (19.14)	-17.3 (3.97)
ETC-1002 180 mg	43	142.6 (28.00)	104.5 (31.40)	-25.2 (23.33)	-24.3 (4.15)

Treatment Comparison	Difference [4]		
	LS Mean (SE)	95% CI	p-value
ETC-1002 120 mg vs. placebo	-13.1 (4.64)	(-22.3, -3.9)	0.0055
ETC-1002 180 mg vs. placebo	-20.1 (4.64)	(-29.3, -10.9)	<0.0001
ETC-1002 180 mg vs. ETC-1002 120 mg	-7.0 (4.68)	(-16.3, 2.3)	0.1366

Source: Table 11 in CSR for Study 1002-009
[1] n is the number of patients with values at both baseline and Week 12 endpoint
[2] Baseline was the mean of the values from Week -1 and Week 0
[3] Week 12 endpoint was the last available post-baseline value
[4] Least-squares mean, SE, 95% CI, and 2-sides p-value are from an analysis of covariance model with terms for treatment and history of statin intolerance and baseline values as a covariance
Abbreviations: CI, confidence interval; LS, least-squares; mITT, modified intent-to-treat; n, number of subjects in group; SE, standard error; SD, standard deviation

Figure 26 presents the mean percent change in LDL-C from baseline over time in the mITT population.

Figure 26. Mean Percent Change From Baseline in LDL-C Over Time, mITT Population

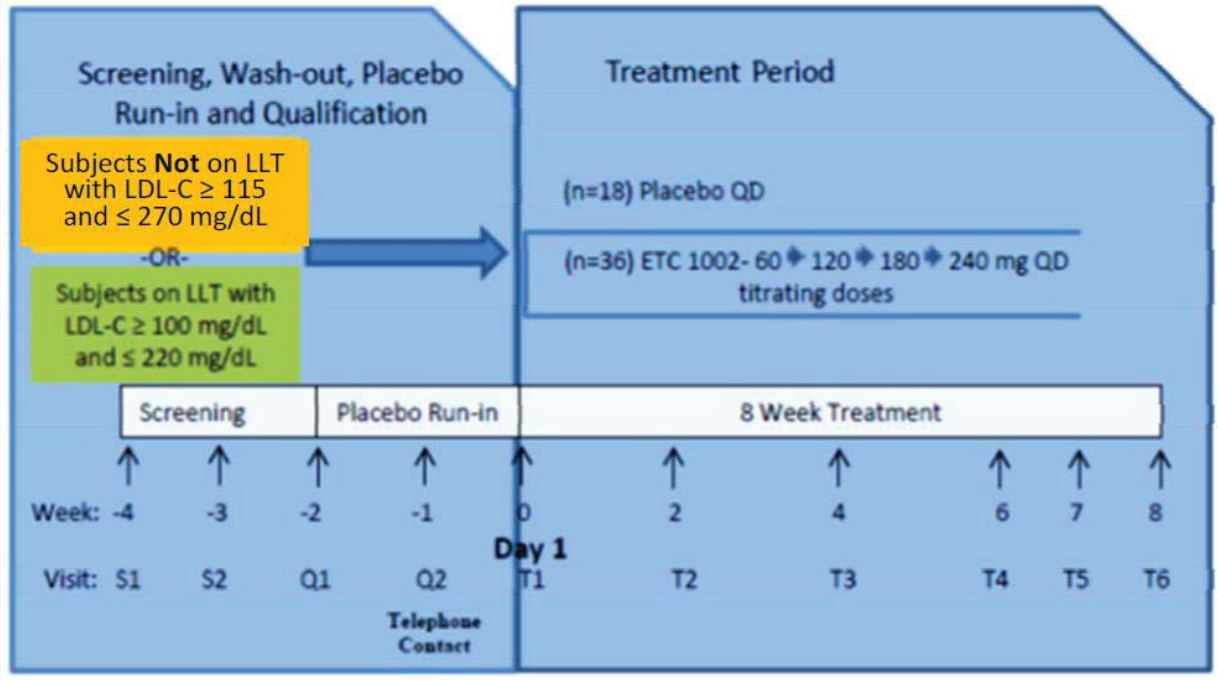


Source: Figure 2 in CSR for Study 1002-009
Baseline is defined as the mean of the values from Week -1 and Week 0
Abbreviations: LDL-C, low-density lipoprotein cholesterol; mITT, modified intent-to-treat

Study 1002-005 was a phase 2, randomized, double-blind (subject, site, and sponsor), placebo-controlled, parallel-group study that was conducted at a single phase 1 clinical unit. Subjects were to be randomized to receive with equal probability of either ETC-1002 80 mg or placebo QD (1:1) for 14 days. Subjects randomized to ETC-1002 were titrated up to 120 mg QD on Days 15 to 28 and subjects randomized to placebo continued on placebo.

Study 1002-006 was a placebo-controlled, randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of ETC-1002 in subjects with hypercholesterolemia and a history of statin intolerance. Eligible subjects were randomized to receive ETC-1002 or placebo (2:1 ratio). Subjects in the ETC-1002 group were initially dosed with 60 mg QD×2 weeks and then titrated successively to 120 mg×2 weeks, 180 mg×2 weeks, and 240 mg×2 weeks. Subjects in the placebo group were dosed with placebo QD for the entire 8 weeks (Figure 27).

Figure 27. Design, Study 1002-006



Abbreviations: LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; n, number of subjects in group; QD, once daily; S, screen visit; T, treatment visit

Table 79 represents the LDL-C lowering effect at Week 2 (for 60 mg QD), Week 4 (for 120 mg QD), Week 6 (for 180 mg QD), and Week 8 (for 240 mg QD). Based on the LDL-C lowering time profile (Figure 26), bempedoic acid reached its maximum effect after 2 weeks. Though Study 1002-006 adopted a forced titration design, the biweekly dose titration and LDL-C evaluation still represented the LDL-C lowering effect at the corresponding dose.

Table 79. Analysis of the Percent Change From Baseline to Weeks 2, 4, 6, and 8 in Calculated LDL-C (mg/dL) (Primary Model), Completers Population

Time Point Treatment Group	N	Baseline[a] / End Point Mean (SE)	LS Mean Percent Change[b] (SE)	Difference from Placebo/ 95% CI	p-value
Week 2					
Placebo	18	183.7 (7.80)/ 179.4 (7.24)	-1.4 (2.52)	--	--
ETC-1002	34	177.3 (6.34)/ 141.5 (5.09)	-19.5 (1.83)	-18.0/ (-24.3, -11.8)	<0.0001
Week 4					
Placebo	15	184.1 (7.20)/ 179.6 (5.17)	-1.0 (2.12)	--	--
ETC-1002	30	177.7 (7.00)/ 121.1 (4.20)	-31.0 (1.50)	-30.0/ (-35.2, -24.7)	<0.0001
Week 6					
Placebo	15	184.1 (7.20)/ 176.5 (7.28)	-3.8 (3.28)	--	--
ETC-1002	31	180.3 (6.51)/ 121.0 (6.21)	-32.6 (2.28)	-28.8/ (-36.9, -20.8)	<0.0001
Week 8					
Placebo	13	179.6 (9.06)/ 169.5 (7.39)	-4.0 (3.51)	--	--
ETC-1002	26	174.8 (7.07)/ 117.2 (5.87)	-32.6 (2.48)	-28.5/ (-37.2, -19.8)	<0.0001

Source: Table 6 in CSR for Study 1002-006
[a] Baseline is defined as the value from Week 0
[b] LS mean percent change from baseline to specified time point based on ANCOVA model with effect of treatment and baseline value as a covariate
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group; NA, not applicable; SE, standard error

Study 1002-007 was a placebo-controlled, randomized, double-blind, parallel-group, drug-interaction study to evaluate the safety of, tolerability of, and effect on atorvastatin pharmacokinetics of ETC-1002 added to atorvastatin 10 mg/day in subjects with hypercholesterolemia. Subjects were randomized to receive ETC-1002 or placebo (3:1 ratio) added to atorvastatin 10 mg QD. Subjects in the ETC-1002 group were initially dosed with 60 mg QD×2 weeks, and then titrated successively to 120 mg×2 weeks, 180 mg×2 weeks, and 240 mg×2 weeks.

Table 80 represents the LDL-C lowering effect at Week 2 (for 60 mg QD), Week 4 (for 120 mg QD), Week 6 (for 180 mg QD), and Week 8 (for 240 mg QD).

Table 80. Analysis of Percent Change From Baseline to Weeks 2, 4, 6, and 8 in Calculated LDL-C (mg/dL) (Primary Model), Completers Population

Time Point Treatment Group	N	Baseline[a] / End Point Mean (SE)	LS Mean Percent Change[b] (SE)	Difference from Placebo/ 95% CI	p-value
Week 2					
Placebo	16	104.2 (7.04)/ 94.6 (7.80)	-9.5 (3.78)	NA	NA
ETC-1002	42	107.0 (4.82)/ 96.3 (4.11)	-8.6 (2.33)	0.9/ (-8.0, 9.8)	0.8403
Week 4					
Placebo	15	102.3 (7.26)/ 95.5 (5.21)	-5.3 (4.41)	NA	NA
ETC-1002	40	107.1 (5.06)/ 89.6 (4.67)	-14.9 (2.70)	-9.6/ (-20.0, 0.8)	0.0689
Week 6					
Placebo	13	104.1 (8.30)/ 94.9 (6.49)	-7.5 (5.31)	NA	NA
ETC-1002	40	108.2 (4.93)/ 88.6 (5.05)	-17.1 (3.03)	-9.6/ (-21.9, 2.7)	0.1231
Week 8					
Placebo	14	102.9 (7.78)/ 97.4 (5.33)	-3.3 (4.87)	NA	NA
ETC-1002	39	108.9 (5.01)/ 83.9 (4.70)	-21.7 (2.91)	-18.4/ (-29.8, -7.0)	0.0021

Source: Table 14 in CSR for Study 1002-007
[a] Baseline is defined as the value from Week 0
[b] LS mean percent change from baseline to specified time point based on ANCOVA model with effect of treatment and baseline value as a covariate
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group; NA, not applicable; SE, standard error

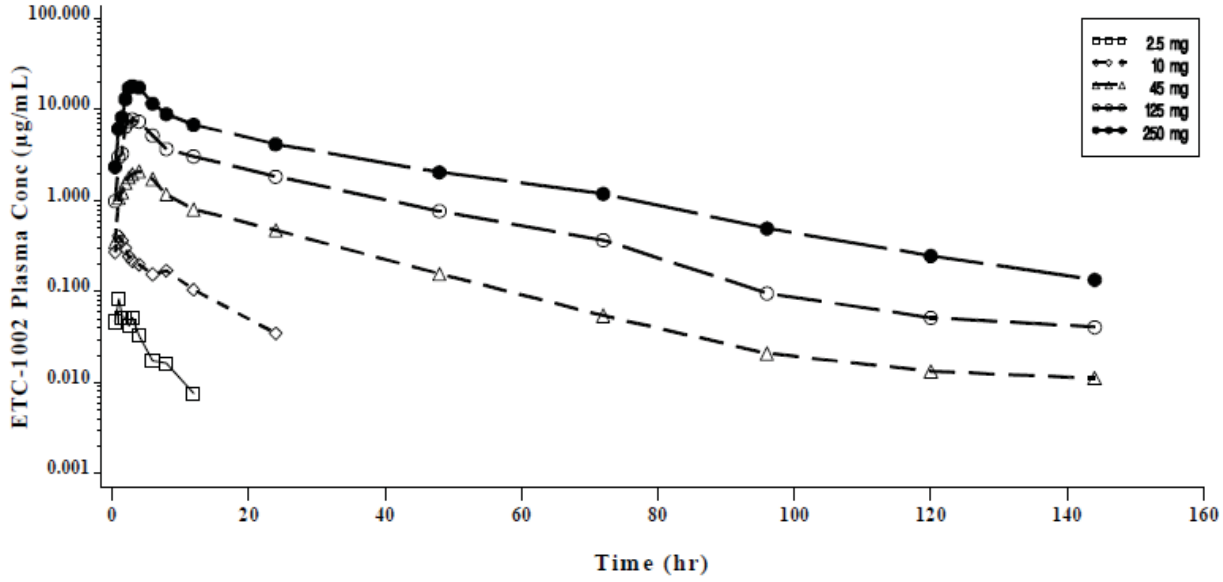
14.2.2. Mass Balance Study (Study 1002-011)

An oral solution of [^{14}C]- bempedoic acid 240 mg was administered in six male healthy volunteers. Of the total radioactive dose administered, 62.1% was recovered from urine and 25.4% from feces over 24 hours, indicating renal clearance was the main route of elimination for total radioactivity. Eighteen subjects received bempedoic acid, with six subjects each being exposed to single doses of bempedoic acid 2.5, 10, 45, 125, or 250 mg.

14.2.3. Single- and Multiple-Dose Ascending Studies (Studies 1002-001, 1002-002, 1002-004)

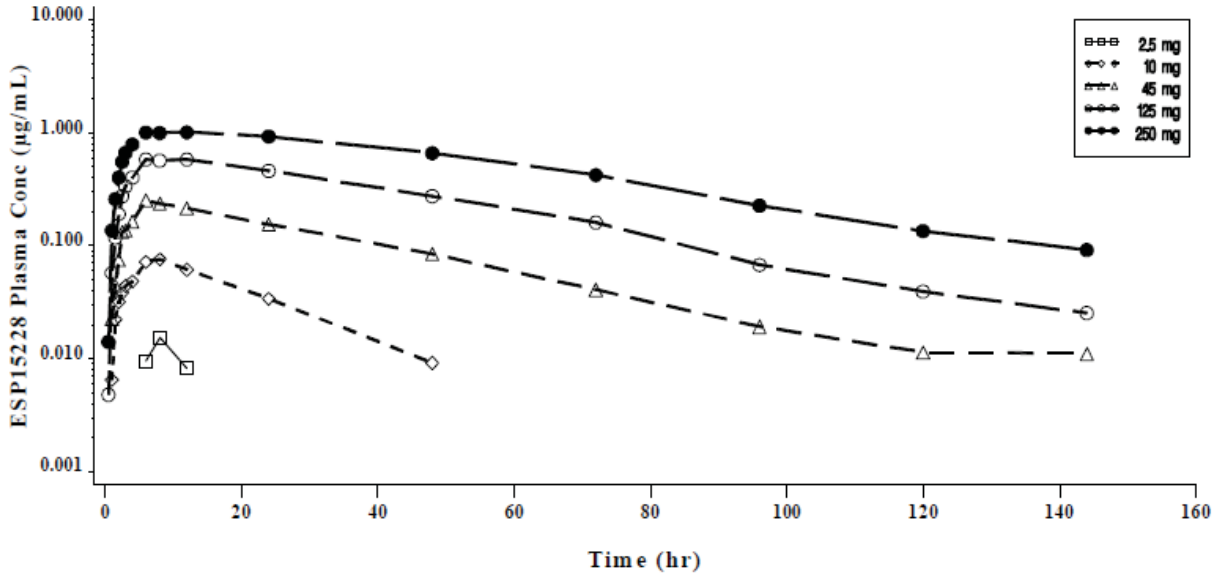
Study 1002-001 was a randomized, double-blind (sponsor open), single ascending-dose study in healthy subjects. In each of two cohorts, nine subjects were randomized 1:1:1 ratio to one of three treatment sequences, with each sequence including two different dose levels of bempedoic acid and a dose of placebo. The mean PK profiles for ETC-1002 and ESP15228 are depicted in Figure 28 and Figure 29.

Figure 28. Log Mean Concentration-Time Profiles for ETC-1002 Following a Single Oral Dose of ETC-1002 Capsules



Source: Figure 3 in CSR for Study 1002-001

Figure 29. Log Mean Concentration-Time Profiles for ESP15228 Following a Single Oral Dose of ETC-1002 Capsules



Source: Figure 4 in CSR for Study 1002-001

Study 1002-002 was a randomized, double-blind (sponsor open), placebo-controlled, ascending multiple-dose study with five cohorts of healthy subjects. Subjects in Cohorts 1 to 4 were randomized 3:1 to receive bempedoic acid (20, 60, 100, or 120 mg, respectively by cohort) or placebo QD for 14 days. Subjects in Cohort 5 were randomized in a 3:1 ratio to receive bempedoic acid 120 mg or placebo QD for 28 days.

Study 1002-004 was a randomized, double-blind (sponsor open), placebo-controlled, ascending multiple-dose study in healthy subjects. Within each dose cohort, eligible subjects were randomized 3:1 to receive bempedoic acid or placebo. Subjects received bempedoic acid 140 mg (Cohort 1), 180 mg (Cohort 2), 220 mg (Cohort 3), or placebo for 14 days. Steady state PK parameters for ETC-1002 and ESP15228 are given in Table 81 and Table 82, and the corresponding concentration time profiles are depicted in Figure 30 and Figure 31.

Table 81. Geometric Mean (%CV) Plasma ETC-1002 Pharmacokinetic Parameters Following Multiple-Dose Administration of ETC-1002 on Day 14: ETC-1002 Plasma PK Parameter Population

Dose (mg)	$C_{max,ss}$ (µg/mL)	T_{max}[a] (hr)	$AUC_{0-24,ss}$ (µg·hr/mL)	Half-life (hr)
140 (Cohort 1)	14.447 (22.7)	3.0 (2.0-3.0)	200.841 (37.6)	26.482 (37.7)
180 (Cohort 2)	19.955 (29.8)	3.5 (2.0-6.0)	277.311 (33.4)	19.240 (53.8)
220 (Cohort 3)	26.548 (23.0)	3.0 (2.0-8.0)	387.589 (33.5)	22.958 (28.6)

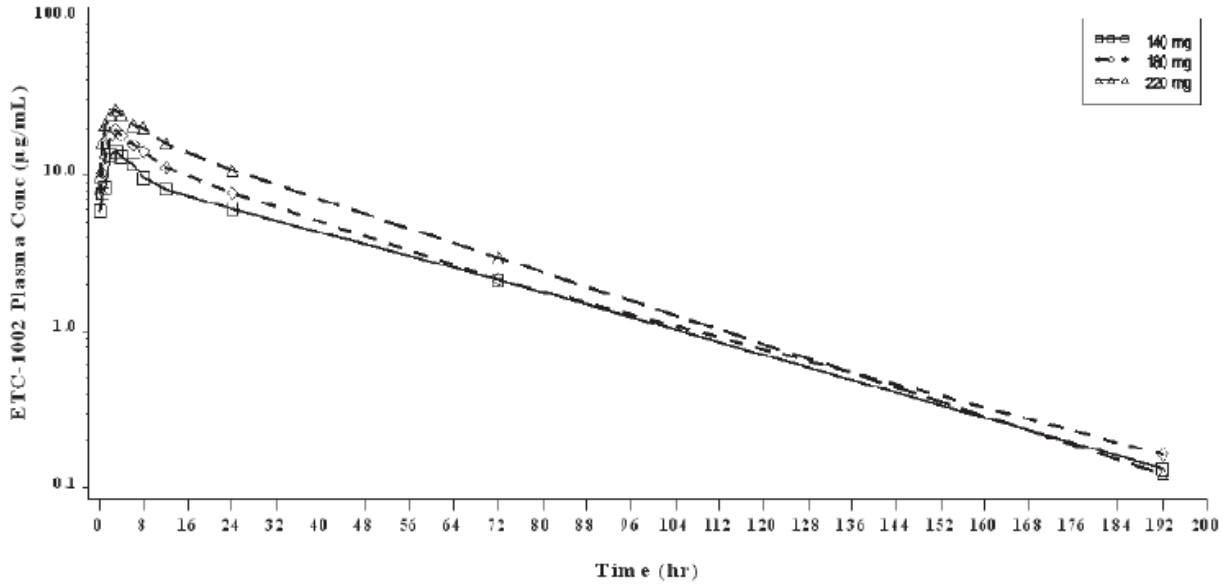
Source: Table 4 in CSR for Study 1002-004
Note: N=6 for all parameters
[a] Median (min-max)
Abbreviations: PK, pharmacokinetics; T_{max}, the time post dose that C_{max} was observed

Table 82. Geometric Mean (%CV) Plasma ESP15228 Pharmacokinetic Parameters Following Multiple-Dose Administration of ETC-1002 on Day 14, ESP15228 Plasma PK Parameter Population

Dose (mg)	$C_{max,ss}$ (µg/mL)	T_{max}[a] (hr)	$AUC_{0-24,ss}$ (µg·hr/mL)	Metabolite Ratio (%)	Half-life (hr)
140 (Cohort 1)	2.333 (35.4)	5.0 (2.0-6.0)	43.753 (43.2)	21.917 (24.3)	33.282 (36.1)
180 (Cohort 2)	2.674 (31.1)	7.0 (6.0-12.0)	48.997 (33.6)	17.748 (20.1)	28.775 (46.7)
220 (Cohort 3)	3.804(35.9)	6.0 (6.0-12.0)	69.677 (38.5)	18.091 (25.5)	29.767 (24.3)

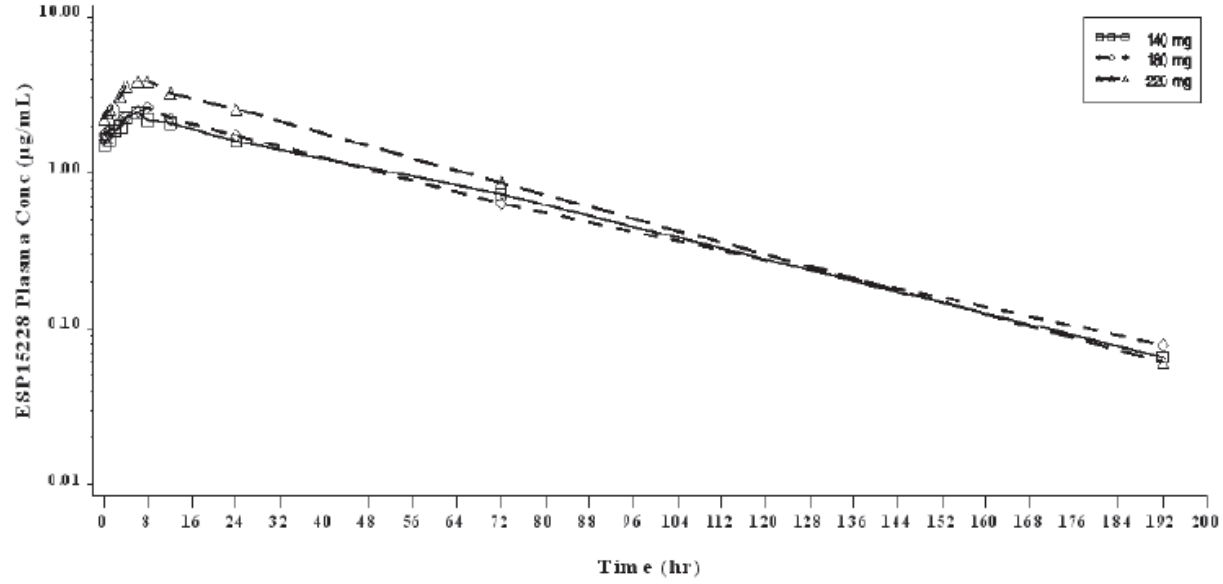
Source: Table 4 in CSR for Study 1002-005
Note: N=6 for all parameters
[a] Median (min-max)
Abbreviations: PK, pharmacokinetics; T_{max}, the time post dose that C_{max} was observed

Figure 30. Log Mean Plasma Concentration-Time Profiles of ETC-1002 Following Multiple-Dose Administration of ETC-1002 on Day 14, ETC-1002 Plasma PK Concentration Population



Source: Figure 2 in CSR for Study 1002-005

Figure 31. Log Mean Plasma Concentration-Time Profiles of ESP15228 Following Multiple-Dose Administration of ETC-1002 on Day 14, ETC-1002 Plasma PK Concentration Population



Source: Figure 3 in CSR for Study 1002-005

14.2.4. Food Effect Study (Study 1002-016)

Study 016 was a randomized, open-label, single-dose, four-sequence, crossover study to evaluate the bioequivalence of capsule and tablet formulation 1 and the food effect on tablet formulation 1 in healthy volunteers. Subjects were randomized to four arms: (1) 180 mg tablet fasted, (2) 180 mg tablet fed, (3) 3×60 mg tablets fasted, and (4) 4×40 mg +1×20 mg capsules fasted. Food had a minimal effect on the bioavailability of the 180 mg tablet.

Table 83. Analysis of Food Effect Comparison of 180-mg Tablet Fed (Test) to 180-mg Tablet Fasted (Reference) Based on ETC-1002 Pharmacokinetic Parameters (ETC-1002 Plasma Pharmacokinetic Parameter Population)

ETC-1002 Pharmacokinetic Parameter	Geometric LS Mean Value		Geometric LS Mean Ratio (Test/Reference)	90% CI for Ratio of LS Means
	1 x 180-mg Tablet Fed [Test] (N=17)	1 x 180-mg Tablet Fasted [Reference] (N=16)		
AUC_{last} (µg·h/mL)	214	218	0.980	(0.931, 1.03)
AUC_{inf} (µg·h/mL)	215	219	0.981	(0.931, 1.03)
C_{max} (µg/mL)	11.1	12.6	0.875	(0.787, 0.973)

Source: Table 10 in CSR for Study 1002-016
Abbreviations: CI, confidence interval; LS, least squares

14.2.5. Comparative Bioavailability (Studies 1002-016 and 1002-036)

Two bioequivalence studies were conducted in healthy volunteers for PK bridging purpose.

See above for the design of Study 1002-016.

Study 1002-036 was a randomized, open-label, single-dose, two-sequence, crossover study to evaluate the bioequivalence between 180 mg tablet formulation 1 and 180 mg tablet formulation 2A.

Study 1002-016 established bioequivalence between capsule and tablet formulation 1. Study 1002-036 established bioequivalence between tablet formulation 1 and tablet formulation 2A.

14.2.6. TQT Study (Study 1002-022)

Study 022 was a randomized, double-blind, parallel-group, placebo- and positive-controlled TQT study in healthy subjects. There were 162 subjects randomized to three treatment arms: (1) bempedoic acid 240 mg + placebo for moxifloxacin, (2) placebo for bempedoic acid and placebo for moxifloxacin, and (3) moxifloxacin 400 mg and placebo. There was no clinically significant QT prolongation liability for bempedoic acid, and no other consistent bempedoic acid–related ECG changes were observed. There was no clinically relevant relationship between bempedoic acid concentration and ddQTcF; the upper confidence boundary (90% CI) was consistently below 10 msec. See Section 17 for QT-IRT review.

14.2.7. Drug Interaction Studies (Studies 1002-012, 1002-017, 1002-031, 1002-037, 1002FDC-049, 1002-007, 1002-035)

Statins

Study 1002-012 was a phase 1, open-label, single-sequence, drug-drug interaction study to assess the effect of steady-state ETC-1002 on the single-dose pharmacokinetics of simvastatin, pravastatin and rosuvastatin in healthy subjects. Thirty-five subjects were administered single doses of statin (simvastatin 20 mg, pravastatin 40 mg, or rosuvastatin 10 mg), followed by bempedoic acid 240 mg QD for 16 days, with a second single dose of statin on Day 12 of bempedoic acid treatment. A weak drug-drug interaction was observed (<2-fold increase of statin AUC) when statins were coadministered with steady-state bempedoic acid. Changes in statin AUC were dependent on the individual statin; increases in AUC of 29% (91%), 99%, and 69% were observed for simvastatin (simvastatin acid), pravastatin, and rosuvastatin, respectively (Table 84 to Table 87).

Table 84. Drug Interaction Evaluation (Simvastatin PK Parameters): Comparison of ETC-1002 240 mg/day + Simvastatin 20 mg (Test) to Simvastatin Alone (Reference)

	Least Squares (LS) Geometric Means			
Simvastatin Parameter	Simvastatin 20 mg (Reference)	ETC-1002 240 mg/day + Simvastatin 20 mg (Test)[a]	Geometric Mean Ratio[b] (T/R)	90% Confidence Interval[b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	20.1	25.9	128.9	95.5 – 174.0
AUC_{last} (ng·h/mL)	19.3	24.8	128.8	94.9 – 174.6
C_{max} (ng/mL)	5.1	5.1	98.7	70.3 – 138.4

Source: Table 11 in CSR for Study 1002-012
[a] Concomitant simvastatin dosing occurred with 12th daily oral dose of ETC-1002 240 mg.
[b] Ratios and confidence intervals are expressed as percentages.
Abbreviations: LS, least squares; PK, pharmacokinetics; T/R, test/reference

Table 85. Drug Interaction Evaluation (Simvastatin Acid PK Parameters): Comparison of ETC-1002 240 mg/day + Simvastatin 20 mg (Test) to Simvastatin Alone (Reference)

	Least Squares (LS) Geometric Means			
Simvastatin Acid Parameter	Simvastatin 20 mg (Reference)	ETC-1002 240 mg/day + Simvastatin 20 mg (Test) [a]	Geometric Mean Ratio [b] (T/R)	90% Confidence Interval [b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	7.1	13.7	191.1	152.4 – 239.7
AUC_{last} (ng·h/mL)	7.0	12.7	180.7	142.7 – 228.8
C_{max} (ng/mL)	0.9	1.2	143.0	116.2 – 176.1

Source: Table 12 in CSR for Study 1002-012
[a] Concomitant simvastatin dosing occurred with 12th daily oral dose of ETC-1002 240 mg.
[b] Ratios and confidence intervals are expressed as percentages.
Abbreviations: LS, least squares; PK, pharmacokinetics; T/R, test/reference

Table 86. Drug Interaction Evaluation (Pravastatin PK Parameters): Comparison of ETC-1002 240 mg/day + Pravastatin 40 mg (Test) to Pravastatin Alone (Reference)

	Least Squares (LS) Geometric Means			
Pravastatin Parameter	Pravastatin 40 mg (Reference)	ETC-1002 240 mg/day + Pravastatin 40 mg (Test)[a]	Geometric Mean Ratio [b] (T/R)	90% Confidence Interval [b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	81.1	160.9	198.5	160.5 – 245.6
AUC_{last} (ng·h/mL)	78.2	152.5	195.0	165.8 – 229.2
C_{max} (ng/mL)	33.4	68.1	203.7	164.5 – 252.3

Source: Table 14 in CSR for Study 1002-012
[a] Concomitant pravastatin dosing occurred with 12th daily oral dose of ETC-1002 240 mg.
[b] Ratios and confidence intervals are expressed as percentages.
Abbreviations: LS, least squares; PK, pharmacokinetics; T/R, test/reference

Table 87. Drug Interaction Evaluation (Rosuvastatin PK Parameters): Comparison of ETC-1002 240 mg/day + Rosuvastatin 10 mg (Test) to Rosuvastatin Alone (Reference)

	Least Squares (LS) Geometric Means			
Rosuvastatin Parameter	Rosuvastatin 10 mg (Reference)	ETC-1002 240 mg/day + Rosuvastatin 10 mg (Test)[a]	Geometric Mean Ratio[b] (T/R)	90% Confidence Interval[b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	32.4	54.8	169.0	152.6 – 187.1
AUC_{last} (ng·h/mL)	29.2	50.0	170.9	156.0 – 187.3
C_{max} (ng/mL)	3.8	8.0	207.7	183.9 – 234.6

Source: Table 16 in CSR for Study 1002-012
[a] Concomitant rosuvastatin dosing occurred with 12th daily oral dose of ETC-1002 240 mg.
[b] Ratios and confidence intervals are expressed as percentages.
Abbreviations: LS, least squares; PK, pharmacokinetics; T/R, test/reference

Study 1002-037 was a phase 1, open-label, single-sequence, drug-drug interaction study to assess the effect of steady-state ETC-1002 on the single-dose pharmacokinetics of atorvastatin 80 mg, simvastatin 40 mg, pravastatin 80 mg, and rosuvastatin 40 mg in healthy subjects. Forty-eight healthy volunteers were assigned to one of four statin cohorts (12 subjects each) on the morning of Day -5 and received a single oral dose of atorvastatin 80 mg, simvastatin 40 mg, pravastatin 80 mg, or rosuvastatin 40 mg. Bempedoic acid 180 mg once daily was administered to all subjects on Days 1 to 16. A single dose of their assigned statin (atorvastatin 80 mg, simvastatin 40 mg, pravastatin 80 mg, or rosuvastatin 40 mg) was administered with the 180-mg dose of bempedoic acid on the morning of Day 12. A weak interaction was identified (1.25 to <2-fold increase in statin AUC) when statin was coadministered with steady-state bempedoic acid.

Table 88. Drug Interaction Evaluation (Simvastatin and Simvastatin Acid Pharmacokinetic Parameters): Comparison of Bempedoic Acid 180 mg/day + Simvastatin 40 mg (Test) to Simvastatin Alone (Reference)

Simvastatin				
Pharmacokinetic Parameter	LS Geometric Means		Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
	Simvastatin 40 mg (Reference)	Simvastatin 40 mg + Steady-State Bempedoic Acid[a] (Test)		
AUC_{inf} (ng·h/mL)	43.0	51.5	119.8	94.1 – 152.4
AUC_{last} (ng·h/mL)	41.4	50.3	121.5	95.6 – 154.5
C_{max} (ng/mL)	8.7	8.7	99.8	74.4 – 133.7
Simvastatin Acid				
Pharmacokinetic Parameter	LS Geometric Means		Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
	Simvastatin 40 mg (Reference)	Simvastatin 40 mg + Steady-State Bempedoic Acid[a] (Test)		
AUC_{inf} (ng·h/mL)	15.7	30.7	195.7	160.7 – 238.3
AUC_{last} (ng·h/mL)	14.8	29.4	199.0	164.6 – 240.6
C_{max} (ng/mL)	1.6	2.4	151.8	121.3 – 189.9

Source: Table 15 in CSR for Study 1002-037
Note: An analysis of variance (ANOVA) on the natural logarithms of AUC_{inf}, AUC_{last}, and C_{max} was performed with cohort as a fixed factor
[a] A single 40-mg dose of rosuvastatin was taken orally with the 12th daily oral 180-mg dose of bempedoic acid
[b] Ratios and confidence intervals are expressed as percentages
Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation

Table 89. Drug Interaction Evaluation (Pravastatin Pharmacokinetic Parameters): Comparison of Bempedoic Acid 180 mg/day + Pravastatin 80 mg (Test) to Pravastatin Alone (Reference)

Pharmacokinetic Parameter	LS Geometric Means		Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
	Pravastatin 80 mg (Reference)	Pravastatin 80 mg + Steady-State Bempedoic Acid[a] (Test)		
AUC_{inf} (ng·h/mL)	290.4	424.1	146.1	122.4 – 174.3
AUC_{last} (ng·h/mL)	286.7	418.8	146.1	124.3 – 171.6
C_{max} (ng/mL)	135.2	183.9	136.0	114.6 – 161.5

Source: Table 17 in CSR for Study 1002-037
Note: An analysis of variance (ANOVA) on the natural logarithms of AUC_{inf}, AUC_{last}, and C_{max} was performed with cohort as a fixed factor
[a] A single 80-mg dose of rosuvastatin was taken orally with the 12th daily oral 180-mg dose of bempedoic acid
[b] Ratios and confidence intervals are expressed as percentages
Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation

Table 90. Drug Interaction Evaluation (Rosuvastatin Pharmacokinetic Parameters): Comparison of Bempedoic Acid 180 mg/day + Rosuvastatin 40 mg (Test) to Rosuvastatin Alone (Reference)

Pharmacokinetic Parameter	LS Geometric Means		Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
	Rosuvastatin 40 mg (Reference)	Rosuvastatin 40 mg + Steady-State Bempedoic Acid[a] (Test)		
AUC_{inf} (ng·h/mL)	128.5	186.9	145.4	121.2 – 174.6
AUC_{last} (ng·h/mL)	123.8	178.1	143.9	119.3 – 173.7
C_{max} (ng/mL)	14.5	24.3	168.2	134.0 – 211.2

Source: Table 19 in CSR for Study 1002-037
Note: An analysis of variance (ANOVA) on the natural logarithms of AUC_{inf}, AUC_{last}, and C_{max} was performed with cohort as a fixed factor
[a] A single 40-mg dose of rosuvastatin was taken orally with the 12th daily oral 180-mg dose of bempedoic acid
[b] Ratios and confidence intervals are expressed as percentages
Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation

Study 1002-007 was a placebo-controlled, randomized, double-blind, parallel-group, drug-interaction study to evaluate the safety of, tolerability of, and effect on atorvastatin pharmacokinetics when ETC-1002 is added to atorvastatin 10 mg/day in subjects with hypercholesterolemia. Subjects were randomized to receive ETC-1002 or placebo (3:1 ratio) added to atorvastatin 10 mg QD. Subjects in the ETC-1002 group were initially dosed with 60 mg QD×2 weeks, and then titrated successively to 120 mg×2 weeks, 180 mg×2 weeks, and 240 mg×2 weeks. Assessment of atorvastatin PK demonstrated a weak interaction based on the mean ratio of less than 2-fold increase for Test to Reference ratio for atorvastatin acid and ortho-hydroxy atorvastatin acid PK parameters following ETC-1002 120 mg/day and 240 mg/day.

Table 91. Drug Interaction Evaluation Based on Atorvastatin Acid Plasma PK Parameters: Atorvastatin Acid Plasma PK Parameter Population

Parameter (Unit)	LS Geometric Means			Ratio of LS Geometric Means [90% CI][a]	
	Atorvastatin 10 mg/day (Reference)	ETC-1002 120 mg/day + Atorvastatin 10 mg/day (Test 1)	ETC-1002 240 mg/day + Atorvastatin 10 mg/day (Test 2)	Test 1/Reference	Test 2/Reference
AUC_{24} (ng·h/mL)	22.7	36.1	40.0	159.4 [145.0, 175.2]	176.7 [160.3, 194.7]
AUC_{last} (ng·h/mL)	22.6	35.9	39.6	158.6 [144.0, 174.8]	175.1 [158.6, 193.2]
C_{max} (ng/mL)	2.7	4.4	4.5	164.7 [142.7, 190.0]	168.5 [145.7, 194.9]

Source: Table 11 in CSR for Study 1002-007
[a] Ratios and Cis are expressed as percentages.
Abbreviations: CI, confidence interval; LS, least squares; PK, pharmacokinetics

Table 92. Drug Interaction Evaluation Based on Ortho-Hydroxy Atorvastatin Acid Plasma PK Parameters: Ortho-Hydroxy Atorvastatin Acid Plasma PK Parameter Population

Parameter (Unit)	LS Geometric Means			Ratio of LS Geometric Means [90% CI][a]	
	Atorvastatin 10 mg/day (Reference)	ETC-1002 120 mg/day + Atorvastatin 10 mg/day (Test 1)	ETC-1002 240 mg/day + Atorvastatin 10 mg/day (Test 2)	Test 1/Reference	Test 2/Reference
AUC_{24} (ng·h/mL)	19.2	29.7	33.7	154.6 [143.7, 166.3]	175.5 [162.7, 189.2]
AUC_{last} (ng·h/mL)	19.2	29.5	33.1	153.5 [141.6, 166.3]	172.4 [158.8, 187.2]
C_{max} (ng/mL)	1.6	2.5	2.8	161.1 [144.7, 179.3]	181.4 [162.7, 202.3]

Source: Table 12 in CSR for Study 1002-007
[a] Ratios and Cis are expressed as percentages.
Abbreviations: CI, confidence interval; LS, least squares; PK, pharmacokinetics

Study 1002-035 assessed the pharmacokinetics, pharmacodynamics and safety of adding ETC-1002 180 mg to atorvastatin 80 mg background therapy in statin-treated patients. Patients were randomized 2:1 to receive either daily bempedoic acid 180-mg tablet or matching placebo tablet in addition to daily doses of atorvastatin 80 mg. A weak interaction was identified. For atorvastatin, ortho-hydroxy atorvastatin, and para-hydroxy atorvastatin, 90% CIs for the test/reference ratios for AUC_{24} and AUC_{last} included values above 125% but not above approximately 200%.

Table 93. Statistical Analysis of Pharmacokinetic Parameters for Atorvastatin

Parameters (Units)	80 mg Atorvastatin + 180 mg ETC-1002 (Test)		80 mg Atorvastatin Alone (Reference)		Test/Reference[c] (%)	90% Confidence Interval[d] (%)
	n[a]	LS Mean[b]	n[a]	LS Mean[b]		
AUC_{24} (hr*ng/mL)	40	301	40	234	129	(98.2, 168)
AUC_{last} (hr*ng/mL)	41	300	41	239	126	(96.5, 164)
C_{max} (ng/mL)	41	65.1	41	65.6	99.4	(73.2, 135)

Source: Table 11-4 in CSR for Study 1002-035
The analyses only include patients who completed both treatment (i.e., 80 mg atorvastatin alone and 80 mg atorvastatin + 180 mg ETC-1002)
[a] n is the number of observations in each treatment used in the model
[b] Least squares mean from ANOVA, calculated by transforming the natural log means back to the linear scale (i.e., geometric mean)
[c] For AUCs and C_{max} ratio of least squares means for natural log transformed parameter (expressed as a percent), natural log transformed back to the linear scale
[d] For AUCx and C_{max} 90% confidence interval for ratio of least squares mean for natural log transformed parameter (expressed as a percent), natural log transformed back to the linear scale
Abbreviations: LS, least square; n, number of subjects in group

Table 94. Statistical Analysis of Pharmacokinetic Parameters for Ortho-Hydroxy Atorvastatin

	80 mg Atorvastatin + 180 mg ETC-1002 (Test)		80 mg Atorvastatin Alone (Reference)			
Parameters (Units)	n[a]	LS Mean[b]	n[a]	LS Mean[b]	Test/Reference[c] (%)	90% Confidence Interval[d] (%)
AUC_{24} (hr*ng/mL)	40	219	40	179	122	(98.0, 153)
AUC_{last} (hr*ng/mL)	41	219	41	184	120	(96.0, 149)
C_{max} (ng/mL)	41	34.8	41	33.8	103	(78.0, 136)

Source: Table 11-5 in CSR for Study 1002-035
The analyses only include patients who completed both treatment (i.e., 80 mg atorvastatin alone and 80 mg atorvastatin + 180 mg ETC-1002)
[a] n is the number of observations in each treatment used in the model
[b] Least squares mean from ANOVA, calculated by transforming the natural log means back to the linear scale (i.e., geometric mean)
[c] For AUCs and C_{max} ratio of least squares means for natural log transformed parameter (expressed as a percent), natural log transformed back to the linear scale
[d] For AUCx and C_{max} 90% confidence interval for ratio of least squares mean for natural log transformed parameter (expressed as a percent), natural log transformed back to the linear scale
Abbreviations: LS, least square; n, number of subjects in group

Table 95. Statistical Analysis of Pharmacokinetic Parameters for Para-Hydroxy Atorvastatin

	80 mg Atorvastatin + 180 mg ETC-1002 (Test)		80 mg Atorvastatin Alone (Reference)			
Parameters (Units)	n[a]	LS Mean[b]	n[a]	LS Mean[b]	Test/Reference[c] (%)	90% Confidence Interval[d] (%)
AUC_{24} (hr*ng/mL)	40	75.2	40	37.1	203	(158, 261)
AUC_{last} (hr*ng/mL)	41	71.7	41	36.6	196	(151, 254)
C_{max} (ng/mL)	41	6.46	41	4.52	143	(102, 200)

Source: Table 11-6 in CSR for Study 1002-035
The analyses only include patients who completed both treatment (i.e., 80 mg atorvastatin alone and 80 mg atorvastatin + 180 mg ETC-1002)
[a] n is the number of observations in each treatment used in the model
[b] Least squares mean from ANOVA, calculated by transforming the natural log means back to the linear scale (i.e., geometric mean)
[c] For AUCs and C_{max} ratio of least squares means for natural log transformed parameter (expressed as a percent), natural log transformed back to the linear scale
[d] For AUCx and C_{max} 90% confidence interval for ratio of least squares mean for natural log transformed parameter (expressed as a percent), natural log transformed back to the linear scale
Abbreviations: LS, least square; n, number of subjects in group

Other Drugs

Study 1002-017 was a phase 1, randomized, open-label, two-sequence, crossover study to assess the steady-state effect of ETC-1002 on the single-dose pharmacokinetics of oral contraceptive tablets in healthy female subjects. Subjects were randomized in a 1:1 ratio to one of two treatment sequences. A single dose of Ortho-Novum 1/35 (ON 1/35) alone was the reference treatment, and a single dose of ON 1/35 administered in combination with steady-state ETC-1002 (ON 1/35 + ETC-1002) was the test treatment. Aside from a small (22%), not clinically meaningful increase in norethindrone C_{max}, no statistically significant effects of steady state bempedoic acid were observed on the PK of a single dose of ON 1/35.

Study 1002-031 was a phase 1, open-label, single-sequence, drug-drug interaction study to assess the effect of steady-state probenecid on the single-dose pharmacokinetics of bempedoic acid in healthy subjects. Twenty subjects received a single oral dose of bempedoic acid 180 mg on Day 1, followed by oral doses of probenecid 500 mg twice daily on Days 6 through 15, and a single oral dose of bempedoic acid 180 mg coadministered with the morning dose of probenecid on Day 11. A weak interaction was identified when a single dose of bempedoic acid was coadministered with steady-state probenecid. ETC-1002 and ESP15228 C_{max} increased 1.2-fold and 1.5-fold, respectively.

Study 1002FDC-049 was an open-label, randomized, two-cohort study to evaluate effect of steady-state bempedoic acid on the single-dose PK of ezetimibe and the effect of steady-state ezetimibe on the single-dose PK of bempedoic acid. Bempedoic acid PK did not change in the presence of steady-state ezetimibe. Ezetimibe glucuronide and total ezetimibe AUC increased approximately 1.6-fold and C_{max} increased 1.8-fold when a single dose of ezetimibe was taken with steady-state bempedoic acid.

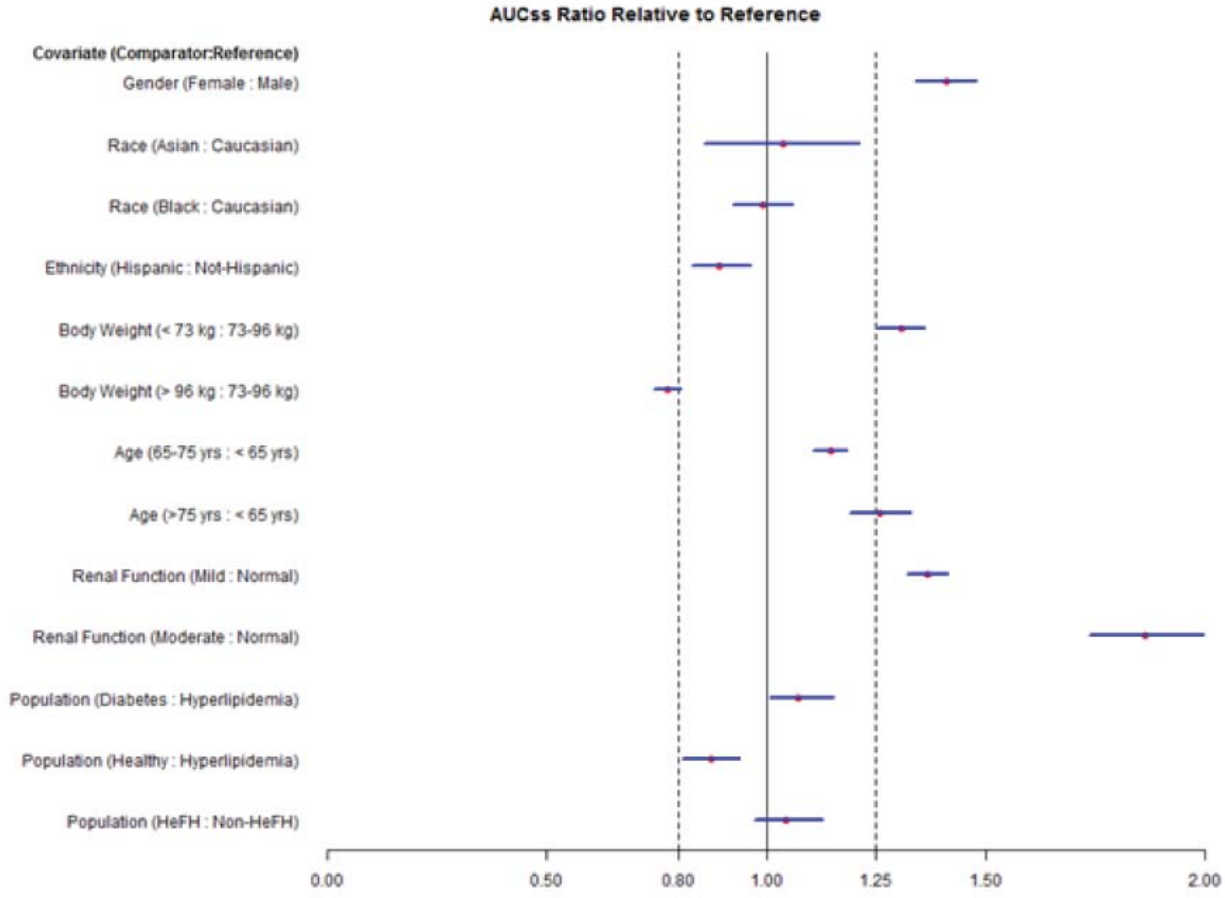
Study 1002-013 was a randomized, double-blind, placebo-controlled, parallel group study of potential effects of steady-state bempedoic acid on the PK of steady-state metformin in patients with type 2 diabetes mellitus (T2DM). On Day -28, patients switched from their current metformin monotherapy (≥850 mg/day, any formulation) to metformin IR 500 mg every 12 hours (Q12H), which they received continuously through Day 14. On Day 1, patients were randomized 3:2 to receive bempedoic acid 180 mg or placebo QD on Days 1 to 15. Metformin steady-state plasma exposure parameters (AUC_{12} and C_{max}) were not statistically significantly different when metformin was administered with or without bempedoic acid. The 90% CIs for the test/reference ratio of the geometric LS means were completely within the prespecified range of 80% to 125%, indicating the lack of a drug-drug interaction.

14.2.8. Intrinsic Factors

14.2.8.1. Age, Race, Sex and Bodyweight

Based on population pharmacokinetic analysis, age, sex, race, and bodyweight had no clinically meaningful impact on the pharmacokinetic characteristics of bempedoic acid (Figure 32). No dose adjustment is recommended.

Figure 32. Influence of Covariate Populations on Predicted Bempedoic Acid Steady-State AUC



Source: Figure 33 in 2.7.2 Summary of Clinical Pharmacology Studies
Red circles show the median ratio of the typical parameter value in the test population compared to the reference as descr bed in the left-hand column. The blue line segments represent the corresponding 90% confidence interval. Vertical dashed lines indicate the interval between ratios of 0.8 to 1.25. Renal function is defined as: normal (eGFR ≥90 mL/min), mild impairment (eGFR ≥60 mL/min and <90 mL/min) and moderate impairment (eGFR ≥30 mL/min and <60 mL/min).
Abbreviations: eGFR, estimated glomerular filtration rate; HeFH, heterozygous familial hypercholesterolemia;

After oral administration, bempedoic acid follows a two-compartment disposition model with a transit absorption compartment and first order elimination.

The following equations describe the covariate-parameter relationships in the bempedoic acid final model:

$$CL_i = TVCL \cdot \left[\frac{WT_i}{83.7}\right]^{\theta_{26}} \cdot \left[\frac{MDRD_i}{89.6}\right]^{\theta_{31}} \cdot (1 + SEXF \cdot \theta_{24}) \cdot (1 + FLGR2 \cdot \theta_{27}) \cdot (1 + FLGD1 \cdot \theta_{29}) \cdot (1 + FLGD2 \cdot \theta_{30}) \cdot (1 + ETHN \cdot \theta_{35}) \cdot exp(\eta_{CL})$$

$$V2_i = TVV2^{(1+SEXF \cdot \theta_{37})} \cdot \left[\frac{BAGE_i}{62}\right]^{\theta_{38}} \cdot \left[\frac{WT_i}{83.7}\right]^{\theta_{39}} \cdot (1 + FLGD1 \cdot \theta_{42}) \cdot exp(\eta_{V2})$$

$$KA_i = TVKA \cdot (1 + FOOD \cdot \theta_8) \cdot exp(\eta_{KA})$$

where parameters are defined as follows:

- TVCL, TVV2, and TVKA are the typical values for steady-state clearance (CL/F), V2/F, and K_a, respectively;
- SEXF is an indicator variable (=1 if female and =0 if male)
- θ_{24} is the fractional change in the typical value of CL/F for females
- θ_{37} is the fractional change in the typical value of V2/F for females
- FLGR2 is an indicator variable (=1 if Black race and =0 otherwise)
- θ_{27} is the fractional change in the typical value of CL/F for Black race
- FLGD1 is an indicator variable (=1 for patients with hyperlipidemia and =0 otherwise)
- θ_{29} is the fractional change in the typical value of CL/F for patients with hyperlipidemia
- θ_{42} is the fractional change in the typical value of V2/F for patients with hyperlipidemia
- FLGD2 is an indicator variable (=1 for patients with T2DM and =0 otherwise)
- θ_{30} is the fractional change in the typical value of CL/F for patients with T2DM
- ETHN is an indicator variable (=1 for subjects of Hispanic/Latino ethnicity and =0 otherwise)
- θ_{35} is the fractional change in the typical value of CL/F for subjects of Hispanic/Latino ethnicity
- FOOD is an indicator variable (=1 for fed administration and =0 otherwise)
- θ_8 is the fractional change in the typical value of KA for administration with food
- θ_{26} is the power to describe the relationship between body weight (WT) and CL/F centered on the median baseline body weight of 83.7 kg
- θ_{31} is the power to describe the relationship between the baseline eGFR (Modification of Diet in Renal Disease Study Equation) and CL/F centered on the median eGFR of 89.6 mL/min
- θ_{39} is the power to describe the relationship between body weight (WT) and V2/F centered on the median body weight of 83.7 kg

The final PK parameter estimates are summarized in Table 96.

Table 96. Pharmacokinetic Parameter Estimates for the Working Full Model

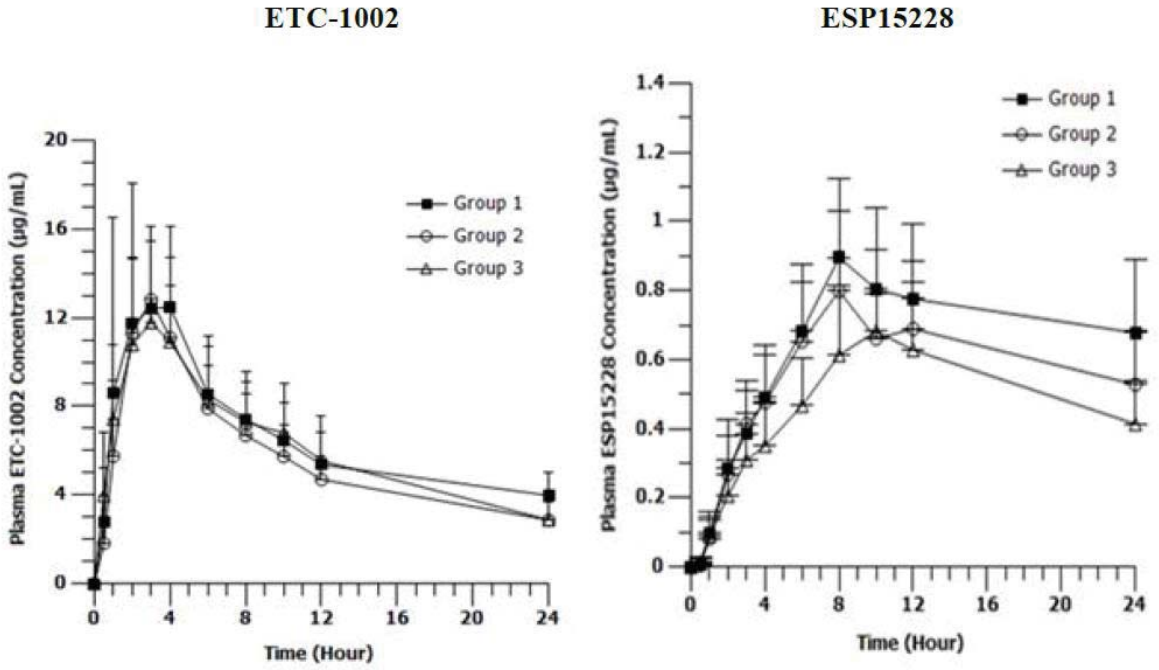
Theta/Parameter	Estimate	ASE	%RSE[a]	95%CI	Units
1 CL/F	0.728	0.0197	2.7	(0.689,0.767)	L/hr
2 V2/F	15.9	1.99	12.5	(12, 19.7)	L
3 Ka	1.43	0.0932	6.5	(1.25, 1.61)	hr-1
6 K23	0.18	0.0264	14.7	(0.128, 0.232)	hr-1
7 K32	0.155	0.00983	6.3	(0.136, 0.174)	hr-1
8 Food on Ka	-0.777	0.012	1.4	(-0.801, -0.754)	
24 Female Sex on CL/F	-0.131	0.0213	16.2	(-0.172, -0.0888)	
26 Body Weight on CL/F	0.637	0.0616	9.7	(0.516, 0.758)	
27 Black Race on CL/F	-0.136	0.0268	19.5	(-0.189, -0.0841)	
29 Hyperlipidemia on CL/F	-0.113	0.0272	24	(-0.167, -0.0598)	
30 T2DM on CL/F	-0.221	0.0293	13.2	(-0.278, -0.163)	
31 eGFR on CL/F	0.558	0.038	6.8	(0.483, 0.632)	
35 Hispanic Ethnicity on CL/F	0.092	0.0358	38.9	(0.0218, 0.162)	
37 Female Sex on V2/F	-0.114	0.0295	25.8	(-0.172, -0.0562)	
38 Age on V2/F	0.604	0.131	21.6	(0.348, 0.86)	
39 Body Weight on V2/F	0.895	0.198	22.1	(0.506, 1.28)	
42 Hyperlipidemia on V2/F	0.192	0.122	63.9	(-0.0483, 0.432)	
Residual Error[a]					
4 RE serial PK sampling	31.9	0.354	1.1	(31.2, 32.6)	%
5 RE sparse PK sampling	54.4	0.697	1.3	(53, 55.8)	%
IIV					
1 CL/F	30.4			(28.4, 32.2)	CV%
2 V2/F	99.1			(92.5, 105)	CV%
3 Ka	73.4			(64.9, 81)	CV%
OFV	-2679.17				

Source: Table 12 in Population Modeling Report 1002-060
[a] Residue error and %RSE are represented as positive values by calculating the square root of (estimate).
Abbreviations: ASE, asymptotic standard error; CI, confidence interval; CL/F, steady-state clearance; eGFR, estimated glomerular filtration rate; F, relative bioavailability; IIV, individual variability; Ka, absorption rate constant; K23, distr bution rate constant (compartment 2 to 3); K32, distribution rate constant (compartment 3 to 2); OFV, objective function value; PK, pharmacokinetic; RE, residual error; RSE, relative standard error; T2DM, type 2 diabetes mellitus; V2/F, apparent distr bution volume of central compartment

14.2.8.2. Hepatic Impairment (Study 1002-032)

Study 032 was an open-label, single dose, parallel group study evaluating the effect of hepatic impairment on the PK of bempedoic acid. A single dose administration of 180 mg bempedoic acid tablet formulation 1 was given to eight subjects with normal hepatic function, eight subjects with mild hepatic function (Child Pugh Class A), and eight subjects with moderate hepatic function (Child Pugh Class B). The mean PK profiles are depicted in Figure 33 for both bempedoic acid (ETC-1002) and ESP15228 (active metabolite).

Figure 33. Arithmetic Mean (+SD) Plasma Bempedoic Acid and ESP15228 Concentration in Subjects With Normal Hepatic Function or Subjects With Mild or Moderate Hepatic Impairment After a Single Oral Dose of Bempedoic Acid 180 mg Through 24 Hours Postdose, Linear Scale



Source: Figure 19 in 2.7.2 Summary of Clinical Pharmacology Studies
Group 1: Normal hepatic function; Group 2: Mild hepatic impairment (Child Pugh Class A); Group:3:Moderate hepatic impairment (Child Pugh Class B)
N=8 subjects per group

Based on the PK results presented above, no dose adjustment in patients with mild or moderate hepatic impairment is recommended.

14.2.8.3. Renal Impairment (Study 1002-023)

Study 023 is an open-label, single-dose, parallel-group study evaluating the effects of renal impairment on the PK of bempedoic acid.

Increases in bempedoic acid exposure were observed with increasing degree of renal impairment. The magnitudes of increase were 48%, 131%, and 137% in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. A descriptive summary of the observed AUC_{inf} and C_{max} in each renal function category is given in Table 97.

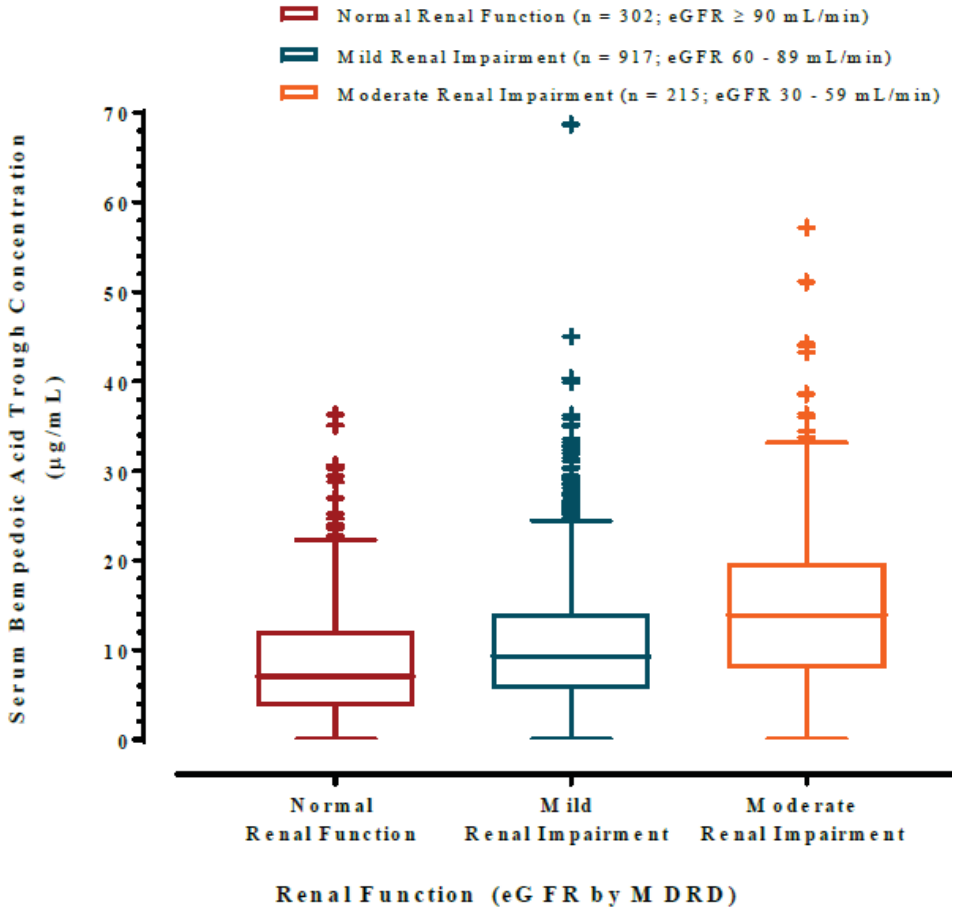
Table 97. Arithmetic Mean (%CV) Plasma Bempedoic Acid Pharmacokinetic Parameters in Subjects by Renal Impairment Category Using eGFR Estimated by MDRD Following Administration of a Single Dose of Bempedoic Acid 180 mg

	Renal Impairment Category by MDRD			
	Normal Function (N = 6)	Mild Impairment (N = 8)	Moderate Impairment (N = 5)	Severe Impairment (N = 5)
AUC_{inf} (µg·h/mL)	187 (31.9)	277 (25.5)	432 (50.7)	444 (35.9)
C_{max} (µg/mL)	9.84 (17.4)	13.8 (20.9)	9.97 (38.5)	12.3 (35.9)

Source: Table 11 in 2.7.2 Summary of Clinical Pharmacology Studies
Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease study equation; N, number of subjects in group

Similarly, observed trough concentrations of subjects with normal renal function, mild and moderate renal impairment from phase 3 studies (Trials 1002-040, 1002-046, 1002-047, and 1002-048) are depicted in Figure 34. Mean bempedoic acid steady-state trough concentrations were approximately 8 and 14 µg/mL in subjects with normal renal function and moderate renal impairment, respectively.

Figure 34. Steady-State, Week 12, Bempedoic Acid Concentration by Renal Impairment Category (MDRD eGFR) for Bempedoic Acid 180 mg QD Regimen Across Pivotal Phase 3 Trials 040, 046, 047, and 048

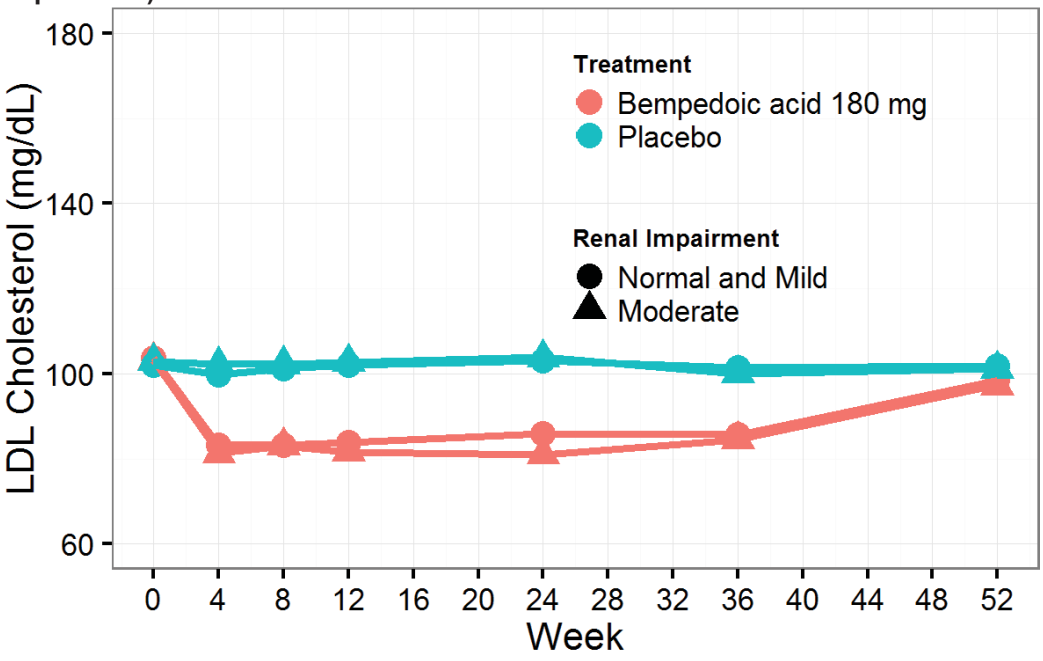


Source: Figure 20 in 2.7.2 Summary of Clinical Pharmacology Studies
Box represents median and interquartile range, whiskers represent 95% of observations; asterisks represent outliers
Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease study equation; QD, once daily

In the target patient population, most patients have mild renal impairment. For example, in phase 3 Trial 040, 16.2% of the patients had moderate renal impairment, and the rest 83.8% had either normal renal function or mild renal function. Therefore, efficacy and safety results from the four pivotal phase 3 studies mainly represented patients with mild renal impairment. To address the necessity of dose adjustment for patients with moderate renal impairment, this reviewer conducted an independent analysis to evaluate the effect of moderate renal impairment on efficacy (LDL-C) and safety (uric acid, eGFR, creatinine, BUN, and hemoglobin) in comparison to patients with normal renal function and mild renal impairment.

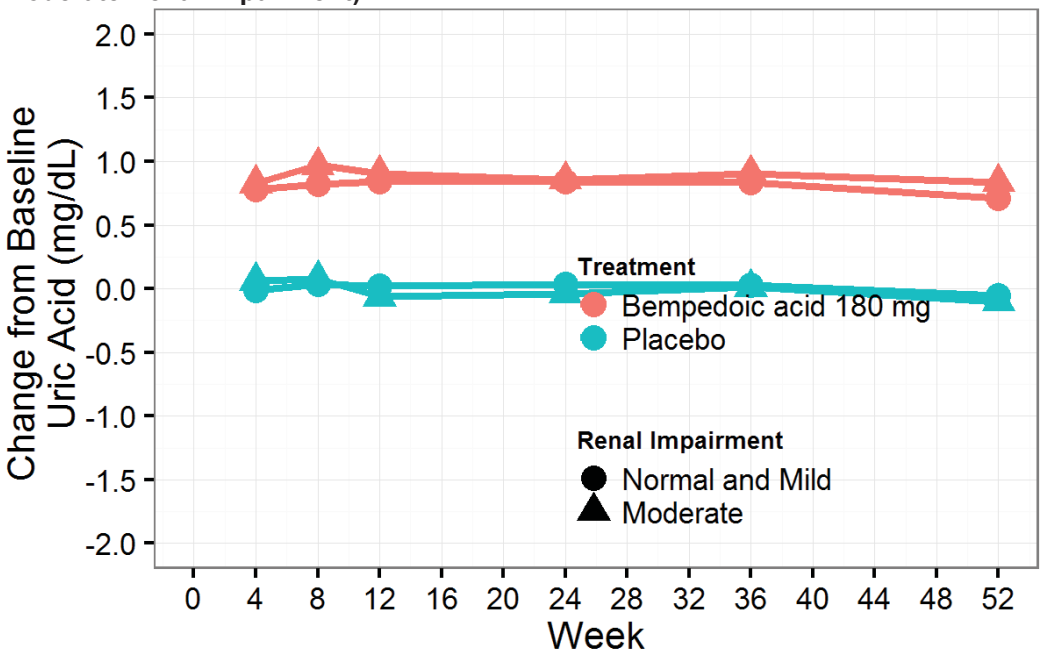
The analysis results are depicted in Figure 35 to Figure 40. Regardless of the differences or indifferences observed in placebo arm between the two renal impairment groups (normal and mild versus moderate), bempedoic acid effects (after adjusting for placebo effect) on LDL-C, uric acid, eGFR, creatinine, BUN, and hemoglobin were consistent between the two renal impairment groups. In conclusion, no additional effect on efficacy or safety was observed in patients with moderate renal impairment. Therefore, from both efficacy and safety perspectives, no dose adjustment is recommended for patients with moderate renal impairment.

Figure 35. Time Course of LDL Cholesterol After Administration of Bempedoic Acid 180 mg or Placebo by Renal Function (Normal Renal Function + Mild Renal Impairment vs. Moderate Renal Impairment)



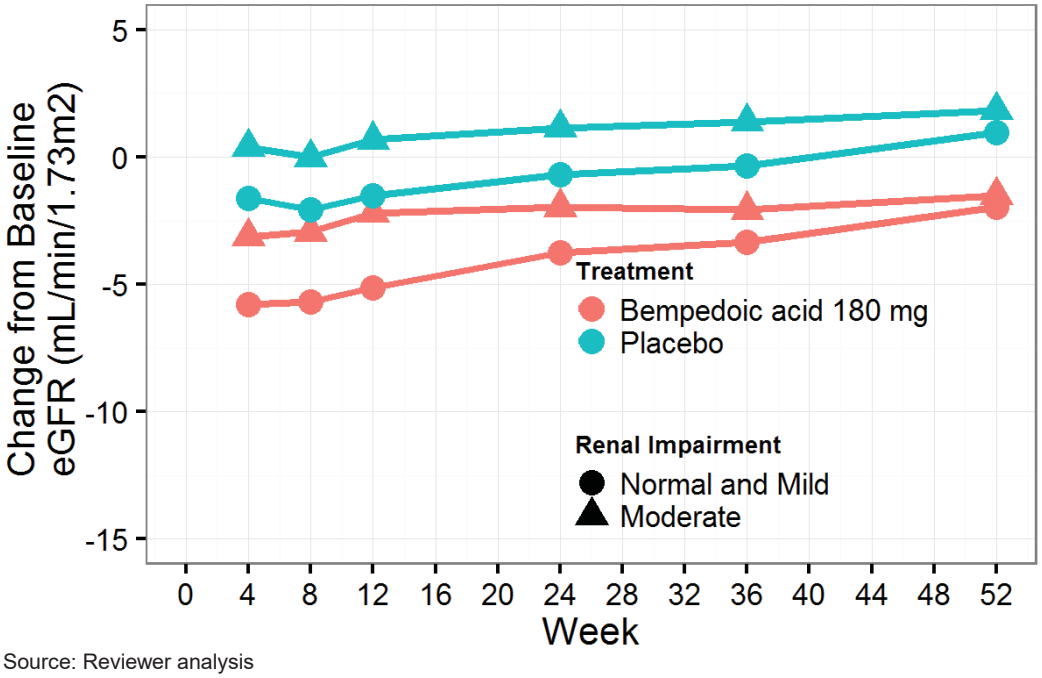
Source: Reviewer analysis
Abbreviations: LDL, low-density lipoprotein

Figure 36. Time Course of Uric Acid Change From Baseline After Administration of Bempedoic Acid 180 mg or Placebo by Renal Function (Normal Renal Function + Mild Renal Impairment vs. Moderate Renal Impairment)



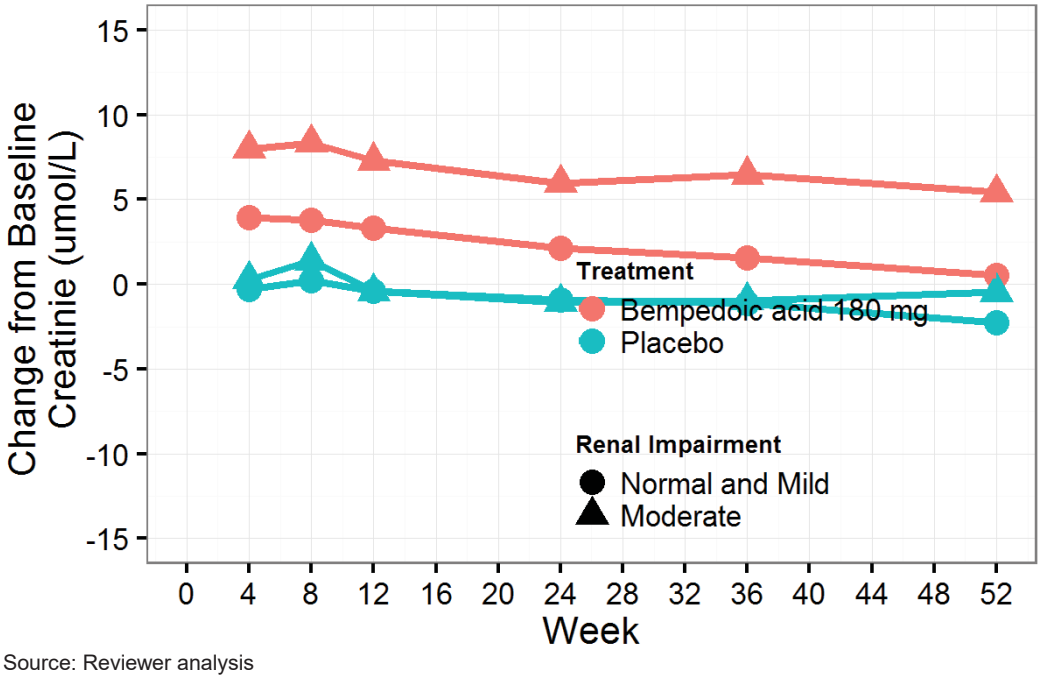
Source: reviewer analysis

Figure 37. Time Course of eGFR Change From Baseline After Administration of Bempedoic Acid 180 mg or Placebo by Renal Function (Normal Renal Function + Mild Renal Impairment vs. Moderate Renal Impairment)



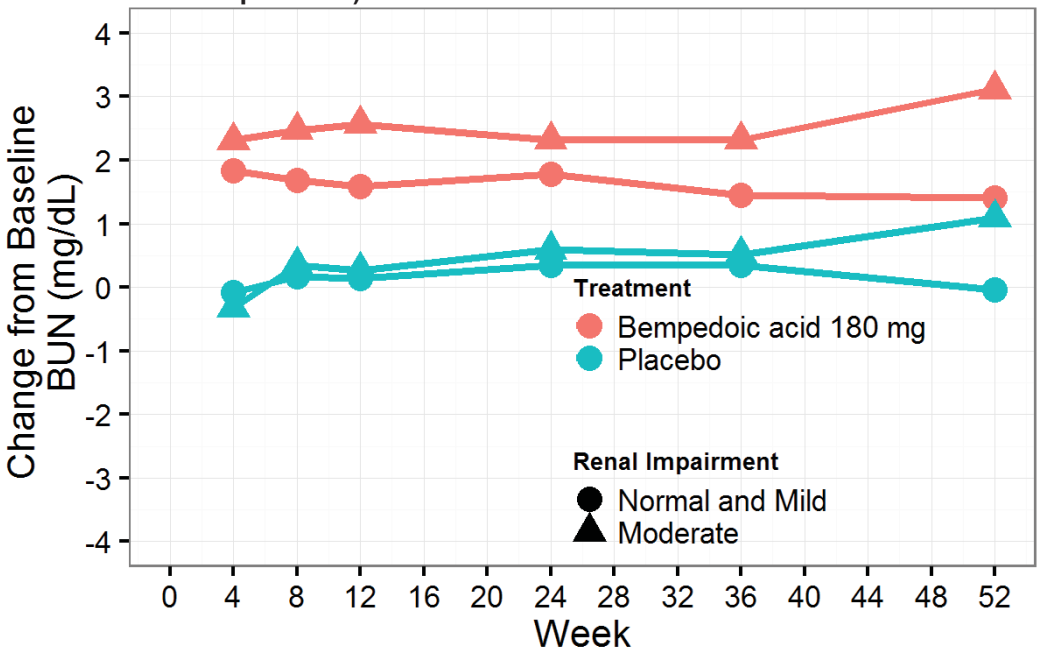
Source: Reviewer analysis
Abbreviations: eGFR, estimated glomerular filtration rate

Figure 38. Time Course of Creatinine Change From Baseline After Administration of Bempedoic Acid 180 mg or Placebo by Renal Function (Normal Renal Function + Mild Renal Impairment vs. Moderate Renal Impairment)



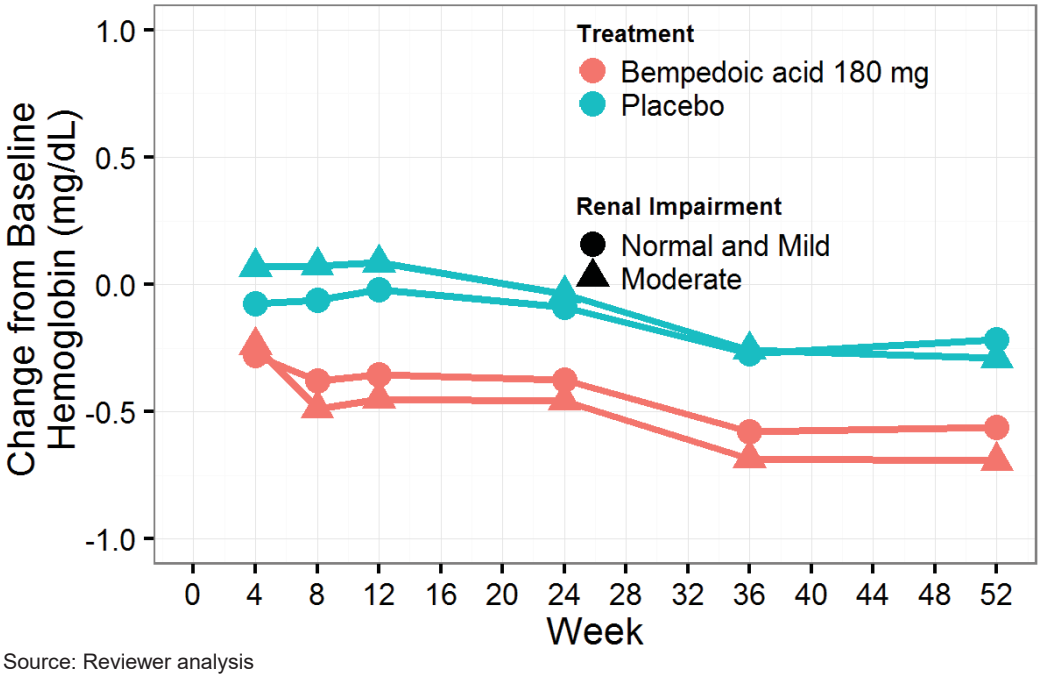
Source: Reviewer analysis

Figure 39. Time Course of Blood Urea Nitrogen (BUN) After Administration of Bempedoic Acid 180 mg or Placebo by Renal Function (Normal Renal Function + Mild Renal Impairment vs. Moderate Renal Impairment)



Source: Reviewer analysis

Figure 40. Time Course of Hemoglobin Change From Baseline After Administration of Bempedoic Acid 180 mg or Placebo by Renal Function (Normal Renal Function + Mild Renal Impairment vs. Moderate Renal Impairment)

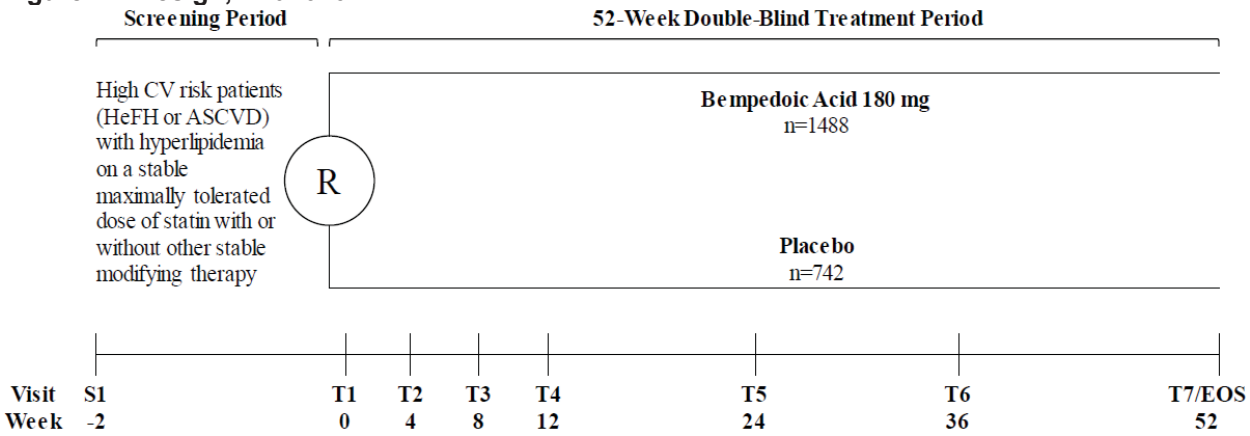


Source: Reviewer analysis

15. Trial Design: Additional Information and Assessment

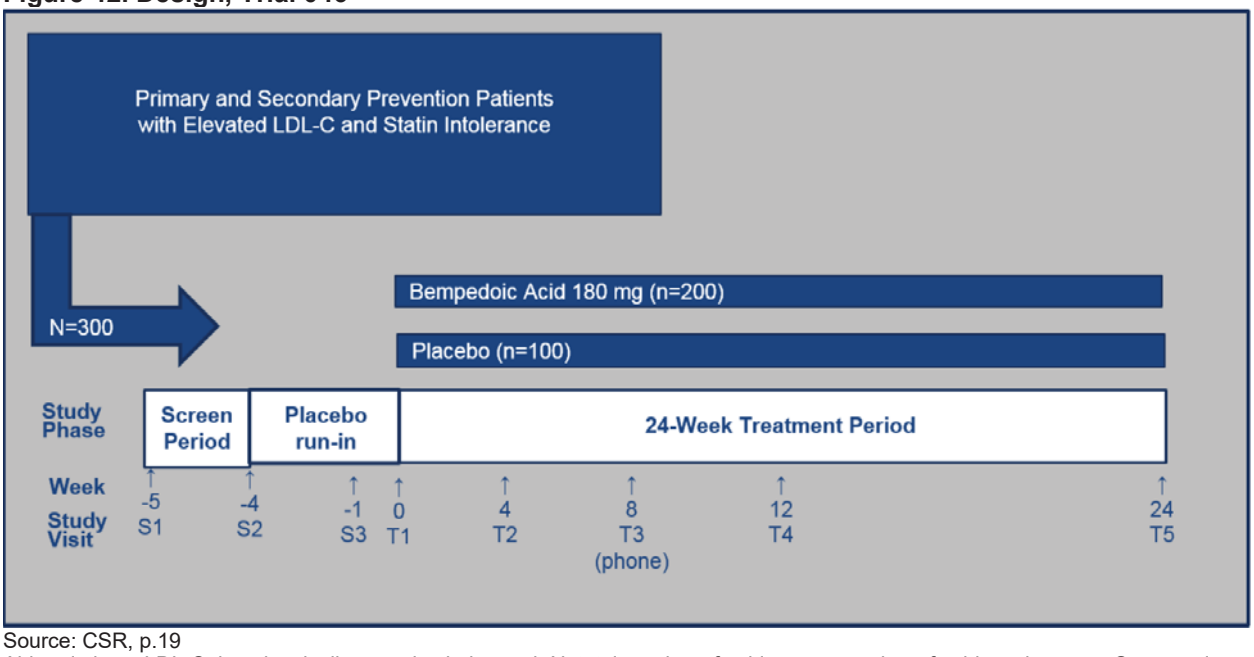
A general schematic description of all four studies is presented below.

Figure 41. Design, Trial 040



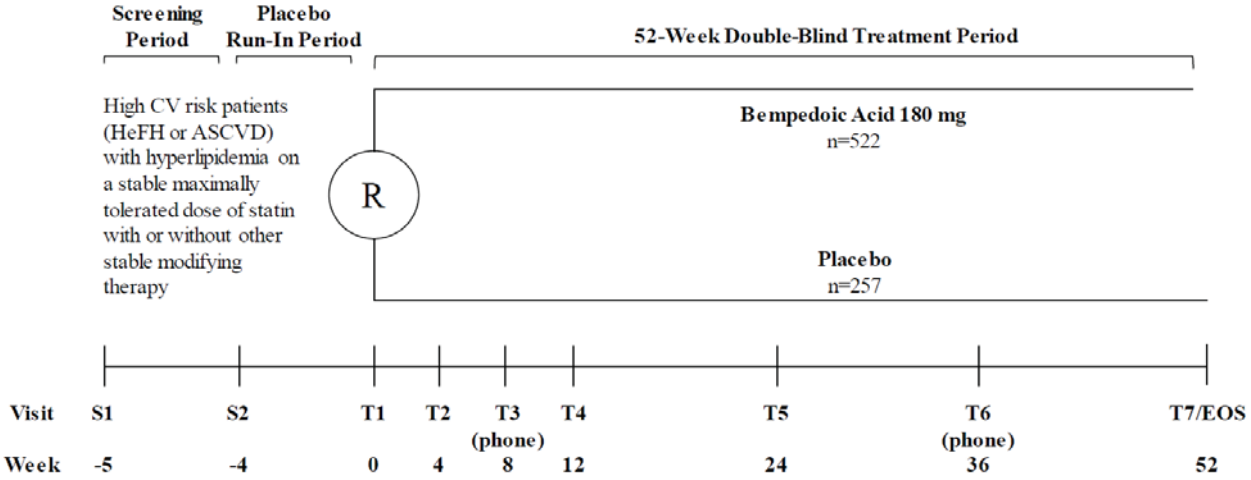
Source: CSR, p.24
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; EOS, end of study; HeFH, heterozygous familial hypercholesterolemia; n, number of subjects in group; R, randomization; S, screening visit; T, treatment visit

Figure 42. Design, Trial 046



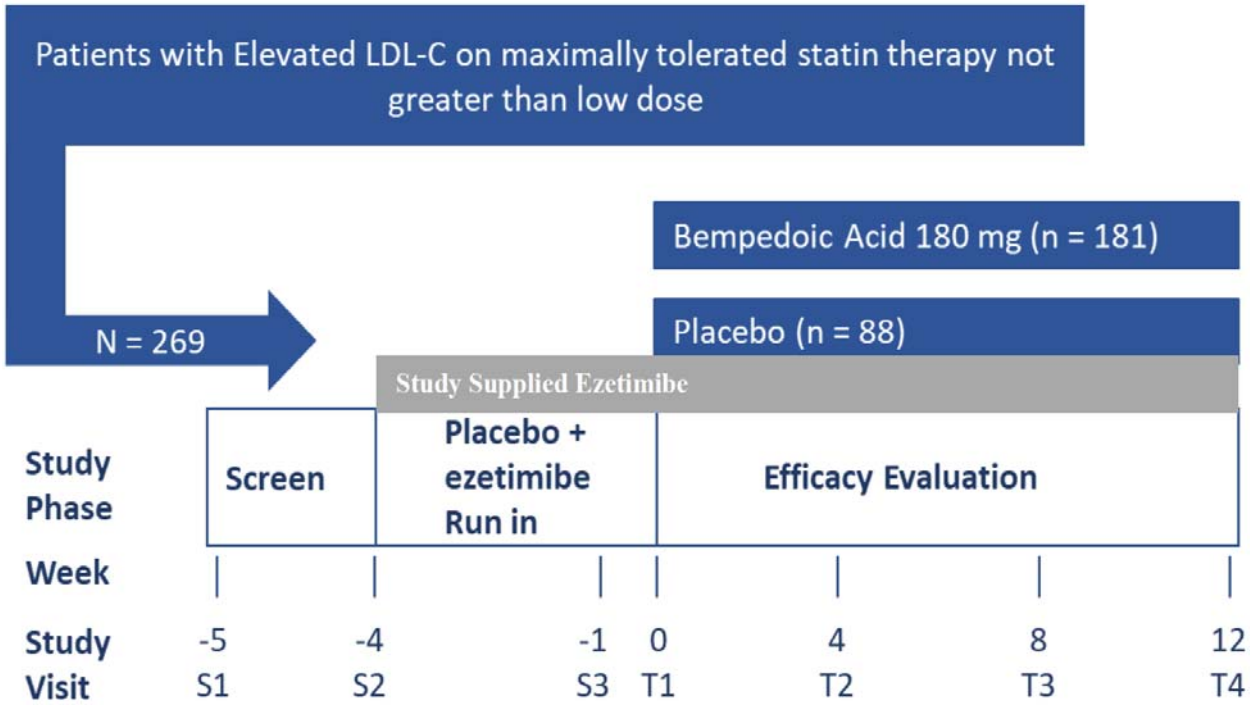
Source: CSR, p.19
Abbreviations: LDL-C, low-density lipoprotein cholesterol; N, total number of subjects; n, number of subjects in group; S, screening visit; T, treatment visit

Figure 43. Design, Trial 047



Source: CSR, p. 24
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; EOS, end of study; HeFH, heterozygous familial hypercholesterolemia; n, number of subjects in group; R, randomization; S, screening visit; T, treatment visit

Figure 44. Design, Trial 048



Source: CSR, p. 20
Abbreviations: LDL-C, low-density lipoprotein cholesterol; N, total number of subjects; n, number of subjects in group; S, screening visit; T, treatment visit

15.1. Trial 040

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Long-Term Safety and Tolerability Study of Bempedoic Acid (ETC-1002) in Patients With Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy (1002-040) (ClinicalTrials.gov No. NCT02666664)
Indication: (b) (4)
Investigational Product: Bempedoic acid
Name of Sponsor: Esperion Therapeutics, Inc.
Publications: None
Investigators and Study Sites: Patients were screened at 116 clinical sites in Canada, Germany, Netherlands, Poland, United Kingdom, and United States, of which 114 sites randomized patients to investigational medicinal product (IMP). A list of investigators by site is provided in Appendix 16.1.4.
Phase of Development: 3
Study Period: Date first patient screened: 21 January 2016 Date last patient completed: 21 February 2018
Background and Rationale for the Study: Cardiovascular disease (CVD) remains the leading cause of death among Americans, Europeans, and other populations around the world (WHO, 2015). An increasing body of evidence suggests that the absolute amount of low-density lipoprotein cholesterol (LDL-C) lowering is proportional to CVD risk reduction by statin and nonstatin therapies that lower LDL-C via upregulation of LDL receptors (Silverman et al, 2016; Cholesterol Treatment Trialists' Collaboration, 2010; Ference et al, 2017). Patients with documented CVD are at very high risk for events and require intensive pharmacologic intervention (Stone et al, 2013). For a variety of reasons, many with CVD are unable to attain aggressive LDL-C treatment goals despite the addition of available lipid-lowering agents to maximally tolerated statin therapy and thus there is an unmet medical need (Jacobson et al, 2014). This Phase 3 study was designed to evaluate the long-term safety, tolerability, and efficacy of bempedoic acid in patients with hyperlipidemia at high risk for cardiovascular (CV) events who had elevated LDL-C and were receiving maximally-tolerated statin therapy with and without other lipid-modifying therapy (LMT). The extended treatment duration (52 weeks) and large patient number (N = 2230) were chosen to obtain robust long-term safety data in this targeted study population of patients who have an unmet medical need for additional lipid lowering.

Objectives: Primary: to evaluate the long-term safety and tolerability of bempedoic acid versus placebo in patients with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular disease [ASCVD]) who were at high risk for a CV event and who had elevated LDL-C, despite receiving treatment with maximally-tolerated statin therapy with and without other LMT. Secondary: to assess percent change from baseline to Week 12 in LDL-C. Tertiary: • to assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive LMT, • to assess high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), and triglycerides (TGs) at Weeks 12, 24, and 52 and, • to assess apolipoprotein B (apo B) and high-sensitivity c-reactive protein (hsCRP) at Weeks 12, 24, and 52.
Methodology: This was a Phase 3, randomized, double-blind, placebo-controlled study evaluating the long-term safety and tolerability of bempedoic acid in patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who were at high risk for a CV event and who had elevated LDL-C, despite receiving treatment with maximally tolerated statin therapy with or without other LMTs. 2-Week Screening Period Screening (Visit S1) occurred approximately 2 weeks prior to Day 1 (Visit T1). Patients who met all enrollment criteria that were assessed at Visit S1 were instructed to continue their existing therapy(s) for lipid regulation and to maintain consistent diet and exercise patterns throughout the study. 52-Week Double-Blind Treatment Period On Day 1, patients meeting eligibility criteria were randomized 2:1 to receive either bempedoic acid 180 mg or placebo once daily (QD) for 52 weeks. Randomization was stratified based on the patient's CV risk and baseline statin dose. Randomized patients were to continue in the study until they completed Week 52 (Visit T7 or End-of Study [EOS] Visit). Randomized patients were to return for clinic visits at Weeks 4, 8, 12, 24, 36, and 52. Patients who discontinued IMP were asked to continue to be followed for safety using the protocol-specified visit schedule and procedures.
Number of Patients Planned: 1950 **Number of Patients Analyzed:** 2230 patients for efficacy (1488 bempedoic acid, 742 placebo) and 2229 patients for safety (1487 bempedoic acid, 742 placebo)
Diagnosis and Main Criteria for Inclusion: Adult men and women (age ≥18 years or legal age of majority based on regional law, whichever was greater) who signed the informed consent document, had a fasting calculated LDL-C ≥70 mg/dL at Visit S1, had a high CV risk defined as either a diagnosis of HeFH or have ASCVD (with established coronary heart disease [CHD] or CHD risk equivalents), and were on stable LMT, including maximally tolerated statin therapy. At Visit S1, patients could not have any recent history (within 3 months prior to Visit S1 or between Visit S1 and randomization) of myocardial infarction, unstable angina leading to hospitalization,

uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of Visit S1), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, transient ischemic attack, endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization); total fasting TGs ≥500 mg/dL; hemoglobin A_{1C} (HbA_{1C}) ≥10%; liver disease or dysfunction; renal dysfunction or nephritic syndrome or a history of nephritis; hematologic or coagulation disorders or a hemoglobin level <10.0 g/dL; or unexplained creatine kinase (CK) >3 × upper limit of normal (ULN) at any time prior to randomization. The complete list of eligibility criteria is provided in Protocol Section 7.

Investigational Medicinal Product, Dose and Mode of Administration, Lot Number: During the double-blind treatment period, bempedoic acid was supplied as 180 mg, film-coated tablets in 35- and/or 100-count (depending on study visit) bottles. The matching placebo was a tablet of identical physical appearance and packaging. IMP was administered by mouth QD with or without food. Lot numbers are provided in Appendix 16.1.6.

Duration of Treatment: Patients were followed in this study for approximately 54 weeks, including 2 weeks for screening and 52 weeks of double-blind treatment.

Study Endpoints:

Safety

The primary safety endpoint for this study was general safety, which includes adverse events (including pre-specified adverse events of special interest (AESIs) as well as adjudicated CV and fatal clinical endpoints), clinical safety laboratories, physical examinations, vital signs, and electrocardiogram (ECGs).

Efficacy

The primary efficacy endpoint was the percent change from baseline to Week 12 in LDL-C. Baseline LDL-C was defined as the mean of the LDL-C values from Week -1 and predose Day 1/Week 0 (last 2 non-missing values on or prior to Day 1).

The key secondary efficacy endpoints included in the hierarchical analysis were:

- percent change from baseline to Week 24 in LDL-C,
- percent change from baseline to Week 12 in non-HDL-C,
- percent change from baseline to Week 12 in TC,
- percent change from baseline to Week 12 in apo B, and
- percent change from baseline to Week 12 in hsCRP.

The following efficacy endpoints were also evaluated:

- percent change or change in LDL-C, HDL-C, TGs, TC, non-HDL-C, hsCRP, and apo B values at other protocol-scheduled time points,
- proportion of patients achieving LDL-C <70 mg/dL at Week 12, 24, and 52, and
- evaluation of patients requiring additional (post-randomization) adjunctive LMT.

Statistical Methods:

The following populations were defined for analysis purposes:

- The Safety Population included all randomized patients who received at least 1 dose of IMP. The Safety Population was used for demographics and baseline characteristics, treatment exposure, concomitant medications, and all safety summaries. Patients in the Safety Population were included in the treatment group that they received, regardless of their randomized treatment.
- The Full Analysis Set (FAS), also known as the intention-to-treat set, included all randomized patients. The FAS was used for all lipid analyses and summaries for disposition, demographics, and baseline characteristics. Patients in the FAS were included in their randomized treatment group.
- The pharmacokinetic (PK) concentration population included all patients in the Safety population who had at least 1 PK assessment. These patients were evaluated for PK concentration summaries unless major protocol deviations were identified that could have affected the data or if key dosing or sampling information was missing.

Safety Analyses:

The primary endpoint for this study was general safety, which included adverse events (including pre-specified adverse events of special interest (AESIs) as well as adjudicated CV and fatal clinical endpoints), clinical safety laboratories, physical examinations, vital signs, and ECGs. All adverse events were coded by system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Affairs Version 20.1. The summarization of adverse events included only treatment-emergent adverse events, defined as adverse events that began or worsened after randomization and the first dose of IMP and up to 30 days after the last dose date of IMP. Clinical CV and fatal endpoints were adjudicated by an independent blinded expert clinical event committee using standardized definitions. Descriptive summaries were produced for all safety endpoints.

Efficacy Analyses:

The primary and key efficacy endpoints were tested sequentially in the order below in a step-down testing procedure to control overall type I error. Each endpoint was tested at an alpha level of 0.05 and tested only if the previous endpoint achieved statistical significance.

1. percent change from baseline to Week 12 in LDL-C (primary efficacy)
2. percent change from baseline to Week 24 in LDL-C
3. percent change from baseline to Week 12 in non-HDL-C
4. percent change from baseline to Week 12 in TC
5. percent change from baseline to Week 12 in apo B
6. percent change from baseline to Week 12 in hsCRP

Efficacy data (actual value, change and percent change from baseline) from all visits was summarized using descriptive statistics with both conventional and standard units. Percent change in LDL-C, non-HDL-C, TC, and apo B were analyzed using an analysis of covariance (ANCOVA) model, with treatment and randomization strata (patient's CV risk and baseline statin dose) as factors, and respective baseline values as a covariate. Baseline values were defined as the average of the last screening and the predose Day 1/Week 0 value.

Missing data for efficacy endpoints was imputed using a pattern-mixture model as described in SAP Section 5.3.2. The ANCOVA output included the least square (LS) mean and standard error (SE) for each treatment group, along with the placebo-correct LS mean and its 95% CI and p value.

Sensitivity analyses of the primary efficacy endpoint included an on-treatment analysis and analyses using observed data only, derived randomization strata instead of the strata recorded by the interactive web response system, and excluding patients who initiated additional LMT prior to Week 12.

For hsCRP, a non-parametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and CI was performed.

RESULTS:

Patient Disposition:

Screened: 3395 patients

Randomized: 2230 patients (1488 bempedoic acid, 742 placebo)

Discontinued IMP: 345 (23.2%) bempedoic acid, 142 (19.1%) placebo

Withdrew from study: 84 (5.6%) bempedoic acid, 36 (4.9%) placebo

Demographic and Baseline Characteristics:

Sex: 1628 (73.0%) men, 601 (27.0%) women

Mean (SD) age: 66.1 (8.96) years

Race: 95.9% White, 2.6% Black or African American, 1.0% Asian, 0.3% Other, 0.1% American Indian or Alaska Native, 0.1% Native Hawaiian or Other Pacific Islander

Ethnicity: 98.4% not Hispanic or Latino; 1.6% Hispanic or Latino

Mean (SD) LDL-C: 103.16 (29.436) mg/dL

Efficacy Results: In patients on maximally tolerated statins with or without other LMTs, treatment with bempedoic acid 180 mg QD resulted in significantly greater percent reductions from baseline at Week 12 in LDL-C (-16.5%) compared with placebo (1.6%). The difference from placebo in LS means (-18.1%) was statistically significant ($p < 0.001$). Absolute mean changes from baseline to Week 12 in LDL-C were -19.23 and 0.43 mg/dL in the bempedoic acid and placebo groups, respectively (observed data). Based on an on-treatment analysis that included only data collected during the treatment period (ie, up to the date of last IMP dose + 7 days), treatment with bempedoic acid resulted in greater LS mean percent reductions from baseline to Week 12 for LDL-C (-18.1%) compared with placebo (1.6%); the difference in LS means was -19.8% (95% CI: -21.7, -17.8) and statistically significant ($p < 0.001$). Differences from placebo for bempedoic acid in LDL-C reductions were also significant for the secondary endpoint at Week 24 ($p < 0.001$), were durable over 52 weeks, and did not vary by the intensity of background statin therapy or a range of baseline subgroups. Bempedoic acid also demonstrated significant treatment effects compared with placebo based on key secondary efficacy analyses at Week 12 for non-HDL-C, TC, apo B, and hsCRP ($p < 0.001$ for all). In the on-treatment analyses, there were greater reductions with bempedoic acid in LDL-C (-19.4% [-21.5, -17.3]) at Week 24, and non-HDL-C (-14.5% [-16.3, -12.8]), TC (-12.2% [-13.5, -10.8]), apo B (-12.9% [-14.5, -11.2]), and hsCRP (-22.6% [-28.2, -17.0]) at Week 12, all compared with placebo (all $p < 0.001$).

Primary and secondary efficacy analyses in the FAS based on the percent change from baseline are summarized below:

Parameter % Change from Baseline	Placebo (N = 742)	Bempedoic Acid (N = 1488)	Difference (Bempedoic Acid vs Placebo)		
			LS Means (SE)	95% CI	P value
LDL-C at Week 12, n	742	1488	-	-	-
LS mean (SE)	1.6 (0.86)	-16.5 (0.52)	-18.1 (1.01)	-20.0, -16.1	<0.001
LDL-C at Week 24, n	742	1488	-	-	-
LS mean (SE)	1.2 (0.88)	-14.9 (0.60)	-16.1 (1.07)	-18.2, -14.0	<0.001
Non-HDL-C at Week 12, n	742	1488	-	-	-
LS mean (SE)	1.5 (0.76)	-11.9 (0.48)	-13.3 (0.90)	-15.1, -11.6	<0.001
TC at Week 12, n	742	1488	-	-	-
LS mean (SE)	0.8 (0.57)	-10.3 (0.37)	-11.1 (0.69)	-12.5, -9.8	<0.001
apo B at Week 12, n	736	1485	-	-	-
LS mean (SE)	3.3 (0.70)	-8.6 (0.47)	-11.9 (0.85)	-13.6, -10.2	<0.001
hsCRP at Week 12, n	724	1421	-	-	-
Median (IQR)	2.6 (91.9)	-22.4 (72.5)	-21.5 (2.80)[a]	-26.96, -16.00	<0.001

apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; LS = least square; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol

Note: Percent change from baseline for LDL-C, non-HDL-C, TC and apo B was analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (HeFH vs. ASCVD, and high intensity statin vs. other statin) as factors and baseline lipid parameter as a covariate. For LDL-C, non-HDL-C and TC, baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1); for apo B and hsCRP, baseline was defined as the last value prior to first dose of IMP. Missing data for LDL-C, non-HDL-C, TC and apo B were imputed through multiple imputation using a pattern mixture model (PMM) accounting for treatment adherence. Analysis for hsCRP was based on Wilcoxon rank sum test and Hodges-Lehmann estimates for location shift and CI; median (IQR) was presented within each treatment group.

The Full Analysis Set (FAS) consisted of all randomized patients.

[a] Location shift

Safety Results: Bempedoic acid was safe and well-tolerated in patients on maximally tolerated statins with and without other LMTs with a safety profile similar to that observed for placebo.

- Most patients had ≥1 treatment-emergent adverse event with similar frequencies across the treatment groups (78.5% bempedoic acid, 78.7% placebo). The 2 most frequently occurring adverse events by preferred term were higher in placebo and included nasopharyngitis (9.8% bempedoic acid, 11.7% placebo) and urinary tract infection (4.8% bempedoic acid, 6.3% placebo), with the third highest being myalgia (6.0% bempedoic acid, 6.1% placebo). Overall, the frequencies of the most common preferred term events were balanced across the treatment groups, with no notable increases in the bempedoic acid group.
- Similar percentages of patients across the treatment groups experienced ≥1 of the following: serious adverse events (14.5% bempedoic acid, 14.0% placebo), IMP-related adverse events (27.0% bempedoic acid, 24.7% placebo), and IMP-related serious adverse events (0.2% bempedoic acid, 0.4% placebo).
- Most adverse events were mild (22.9% bempedoic acid, 26.4% placebo) to moderate (43.2% bempedoic acid, 42.9% placebo) in severity. Adverse events considered severe in

intensity occurred in 12.4% compared with 9.4% of patients in the bempedoic acid and placebo groups, respectively.

- Thirteen patients (0.9%) in the bempedoic acid group and 2 patients (0.3%) in the placebo group had adverse events with a fatal outcome within 30 days of the last dose of IMP. None of the fatal adverse events were considered related to IMP by the investigator or the Sponsor. The 0.6% difference in frequency between the 2 groups was driven primarily by an increased frequency of events in the Cardiac disorders (0.3% bempedoic acid, 0% placebo) and Neoplasms benign, malignant and unspecified (incl cysts and polyps) (0.3% bempedoic acid, 0% placebo) SOCs. Medical review of individual cases did not reveal any safety signal associated with fatal adverse events and bempedoic acid treatment. The frequency of adverse events in the Cardiac disorder SOC (10.6% bempedoic acid, 11.6% placebo), serious adverse events in the Cardiac disorder SOC (5.2% bempedoic acid, 5.7% placebo), positively-adjudicated CV and fatal clinical events (4.6% bempedoic acid, 5.7% placebo), and adverse events in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC (3.4% bempedoic acid, 2.4% placebo) were balanced across the treatment groups. Further, these patients had significant medical histories and comorbidities related to these events as well as other risk factors that likely contributed to the fatalities. The rate and types of fatal events was consistent with expectations relative to the very high-risk patient population and other studies of similar trial design.
- Adverse events leading to discontinuation of IMP occurred in 10.9% and 7.1% of patients in the bempedoic acid and placebo groups, respectively. The difference in frequency was not driven by any single SOC or preferred term. There were no SOCs with an incidence difference >1% between groups.
- AESIs were evaluated based on predefined adverse event preferred terms and, when appropriate, additional adverse event and laboratory data. Results by AESI category included:
    - Metabolic acidosis: adverse events in this AESI category were rare and similar between groups (0.1% bempedoic acid, 0% placebo).
    - Hypoglycemia: adverse events in this AESI category were similar between groups (2.2% bempedoic acid, 3.1% placebo).
    - Hepatic events: adverse events in this AESI category occurred in 2.5% of bempedoic acid patients and 1.5% of placebo patients. By preferred term, only aspartate aminotransferase (AST) increase occurred with a ≥1% difference between groups (1.5% bempedoic acid, 0.4% placebo). Repeat and confirmed increases in AST or alanine aminotransferase (ALT) >3 × ULN occurred in 7 bempedoic acid patients (0.5%) and 1 placebo patient (0.1%). No patient in either treatment group had total bilirubin >2 × ULN or met the criteria for potential Hy's Law.
    - Muscular safety events: adverse events in the AESI category of Muscular disorders occurred in 13.1% of bempedoic acid patients and 10.1% in placebo patients; by preferred term, muscle spasms (4.2% bempedoic acid, 2.7% placebo) and pain in extremity (3.4% bempedoic acid, 2.2% placebo) occurred with ≥1% difference between groups. Myalgia (6.0% bempedoic acid, 6.1% placebo) and muscular weakness (0.6% bempedoic acid, 0.5% placebo) occurred at similar frequencies in both groups. AESIs in the CK elevations category occurred in 2.4% of bempedoic acid patients and 1.8% of placebo patients. Based on laboratory data, repeat and

confirmed postbaseline CK values >5 and >10 × ULN occurred in 0.5% and 0.3% in the bempedoic acid group, respectively, and 0.1% and 0.1% of patients in the placebo group.

- New onset or worsening of diabetes: adverse events in this AESI category occurred in 3.3% of bempedoic acid patients and 5.4% of placebo patients; by preferred term, diabetes mellitus, diabetes mellitus inadequate control, impaired fasting glucose, glycosylated hemoglobin increased, glucose urine present, and glycosuria were reported at least twice as frequently with placebo compared with bempedoic acid. Glucose tolerance impaired was the only preferred terms reported at least twice as frequently with bempedoic acid compared with placebo. Based on laboratory results, there were slight differences in the change in HbA_{1c} between bempedoic acid vs placebo in patients with diabetes at baseline of -0.19% and -0.16% at Weeks 12 and 52, respectively.
- Renal events: bempedoic acid treatment resulted in small increases in serum creatinine associated with small decreases in estimated glomerular filtration rate (eGFR). The patient incidence of adverse events related to eGFR was low overall, but numerically higher with bempedoic acid compared with placebo. Adverse events in this AESI category, which included gout, occurred in 4.0% bempedoic acid patients and 1.3% of placebo patients; the difference in absolute frequency between the groups was largely driven by a higher frequency of gout events in the bempedoic acid group, which is further discussed below with findings of uric acid.
- CV events: any positively-adjudicated MACE or non-MACE occurred in 4.6% of bempedoic acid patients and 5.7% of placebo patients; the difference was driven by a lower patient incidence for bempedoic acid versus placebo for non-fatal myocardial infarction (1.3% bempedoic acid vs 1.8% placebo), coronary revascularization (2.6% vs 3.4%), hospitalization for unstable angina (1.0% vs 1.5%), and non-coronary arterial revascularization (0.3% vs 0.8%).
- Neurocognitive/neurologic events: adverse events in this AESI category were similar between groups (0.7% bempedoic acid, 0.9% placebo).
- Increased uric acid: bempedoic acid treatment resulted in small mean increases in uric acid that were consistent over 52 weeks compared with placebo. A higher percentage of patients in the bempedoic acid group had adverse events of gout, blood uric acid increased, and hyperuricemia (1.2%, 1.3% and 1.0%, respectively) compared with placebo (0.3%, 0.4%, and 0.3%, respectively). For most patients, these events were mild to moderate in severity and managed without interruption or discontinuation of treatment with bempedoic acid.
- Decreased hemoglobin: bempedoic acid treatment resulted in small mean decreases in hemoglobin that were stable over 52 weeks compared with placebo. A higher percentage of patients had decreases ≥2 g/dL from baseline in the bempedoic acid group (9.3%) compared with placebo (4.4%); 2 bempedoic acid patients and 1 placebo patient had decreases in hemoglobin ≥5 g/dL from baseline. Decreases in hemoglobin did not result in a notably higher patient incidence of adverse events of anemia in the bempedoic acid group (2.9%) compared with placebo (2.2%).

- There were no treatment-related changes in other laboratory parameters or vital signs and no clinically significant abnormal shifts in ECGs measurements from baseline to end-of-study.

CONCLUSIONS:

Results from this 52-week, Phase 3, randomized (2:1), double-blind, placebo-controlled study of bempedoic acid 180 mg QD in 2230 patients with hyperlipidemia at high risk for CV events who had elevated LDL-C despite treatment with maximally-tolerated statin therapy with and without other LMTs demonstrated the following:

- Bempedoic acid treatment was well-tolerated with a favorable safety profile. Adverse events with bempedoic acid were generally similar to those with placebo, including the patient incidence and severity of any adverse event, serious adverse event, positively-adjudicated CV or fata clinical events, and AESIs in the metabolic acidosis, hypoglycemia, and neurocognitive/neurologic categories.
- The patient incidence of fatal adverse events and adverse events leading to discontinuation of IMP was low with bempedoic acid. None of the fatal adverse events were considered related to IMP by the investigator or the Sponsor. Medical review of individual cases did not reveal any safety concern associated with bempedoic acid treatment for fatal adverse events or adverse events leading to discontinuation of IMP. The rate and types of fatal events was consistent with expectations relative to the very high risk and older patient population and other clinical trials with a similar trial design.
- The patient incidence of hepatic events (based on AESIs) and repeated and confirmed AST and/or ALT > 3 × ULN were low with bempedoic acid (2.5% and 0.5%, respectively) and similar to that with placebo (1.5% and 0.1%, respectively).
- The patient incidence of CK elevations (based on adverse events and repeated and confirmed CK > 5 × ULN), adverse events of muscular weakness and myalgia, and discontinuations due to muscle-related adverse events were low with bempedoic acid and similar to that with placebo.
- Bempedoic acid treatment resulted in a lower patient incidence of new onset or worsening diabetes adverse events compared with placebo. Correspondingly, there were slight differences in the change in HbA_{1c} between bempedoic acid vs placebo in patients with diabetes at baseline of -0.19% and -0.16% at Weeks 12 and 52, respectively.
- Bempedoic acid treatment resulted in small mean increases in uric acid that were consistent over 52 weeks. A numerically higher patient incidence of adverse events of gout, hyperuricemia, and blood uric acid increased occurred with bempedoic acid (1.0% to 1.3%) compared with placebo (0.3% to 0.4%). For most patients, these events were mild to moderate in severity and managed without interruption or discontinuation of treatment with bempedoic acid.
- Bempedoic acid treatment resulted in small increases in serum creatinine associated with small decreases in eGFR. The patient incidence of adverse events related to eGFR was low overall, but numerically higher with bempedoic acid compared with placebo.
- Bempedoic acid treatment resulted in small mean decreases in hemoglobin that were durable over 52 weeks compared with placebo, with a higher percentage of patients in the bempedoic acid group (9.3%) having decreases of ≥2 g/dL from baseline compared with placebo (4.4%); 2 bempedoic acid patients and 1 placebo patient had decreases in hemoglobin ≥5 g/dL from baseline. Adverse events of anemia occurred in similar proportions in the bempedoic acid group compared with placebo.

- In patients on maximally-tolerated statins with or without other LMTs, treatment with bempedoic acid resulted in significantly greater reductions in LDL-C (-16.5% LS mean percent change from baseline) compared with placebo (1.6%). The difference from placebo in LS means (-18.1%; LS mean difference 95% CI: -20.0, -16.1) was statistically significant ($p < 0.001$). Absolute mean changes from baseline to Week 12 in LDL-C were -19.23 and 0.43 mg/dL in the bempedoic acid and placebo groups, respectively (observed data). Based on an on-treatment analysis that included only data collected during the treatment period (ie, up to the date of last IMP dose + 7 days), treatment with bempedoic acid resulted in significantly greater LS mean percent reductions from baseline to Week 12 for LDL-C (-18.1%) compared with placebo (1.6%); the difference in LS means was -19.8% (-21.7, -17.8; $p < 0.001$). LDL-C reductions were sustained over 52 weeks and did not vary by the intensity of background statin therapy or a range of baseline subgroups.
- The overall treatment benefit of bempedoic acid was also observed across all key secondary endpoints. At Week 24, bempedoic acid significantly reduced LDL-C by 16.1% compared with placebo (LS mean difference 95% CI: -18.2, -14.0; $p < 0.001$). At Week 12, bempedoic acid reduced non-HDL-C by 13.3% (95% CI: -15.1, -11.6), TC by 11.1% (-12.5, -9.8), apo B by 11.9% (-13.6, -10.2), and hsCRP by 21.5% (-27.0, -16.0) compared with placebo (all $p < 0.001$). In the on-treatment analyses, there were greater percent reductions with bempedoic acid in LDL-C (-19.4% [-21.5, -17.3]) at Week 24, and non-HDL-C (-14.5% [-16.3, -12.8]), TC (-12.2% [-13.5, -10.8]), apo B (-12.9% [-14.5, -11.2]), and hsCRP (-22.6% [-28.2, -17.0]) at Week 12, all compared with placebo (all $p < 0.001$).

Date and Version of the Report:

21 December 2018, Final

Source: Applicant

15.2. Trial 047

Title of Study: Long-Term, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients With Hyperlipidemia at High Cardiovascular Risk not Adequately Controlled by Their Lipid-Modifying Therapy (1002-047) (ClinicalTrials.gov No. NCT02991118)
Indication: (b) (4)
Investigational Product: Bempedoic acid
Name of Sponsor: Esperion Therapeutics, Inc.
Publications: None
Investigators and Study Sites: Patients were screened at 91 clinical sites in Canada, Germany, Poland, Ukraine, the United Kingdom, and the United States. A list of investigators by site is provided in Appendix 16.1.4.
Phase of Development: 3
Study Period: Date first patient screened: 18 November 2016 Date last patient completed: 22 September 2018
Background and Rationale for the Study: Cardiovascular disease (CVD) remains the leading cause of death among Americans, Europeans, and other populations around the world (WHO, 2015). An increasing body of evidence suggests that the absolute amount of low-density lipoprotein cholesterol (LDL-C) lowering is proportional to CVD risk reduction by statin and nonstatin therapies that lower LDL-C via upregulation of LDL receptors (Silverman et al, 2016; Cholesterol Treatment Trialists' Collaboration, 2010; Ference et al, 2017). Patients with documented CVD are at very high risk for events and require intensive pharmacologic intervention (Stone et al, 2013). For a variety of reasons, many with CVD are unable to attain aggressive LDL-C treatment goals despite the addition of available lipid-lowering agents to maximally tolerated statin therapy and thus there is an unmet medical need (Jacobson et al, 2014). This Phase 3 study was designed to evaluate the long-term safety, tolerability, and efficacy of bempedoic acid in patients with hyperlipidemia at high risk for cardiovascular (CV) events who had elevated LDL-C and were receiving maximally-tolerated statin therapy with and without other lipid-modifying therapy (LMT). The extended treatment duration (52 weeks) and large patient number (N = 779) were chosen to obtain robust long-term safety data in this targeted study population of patients who have an unmet medical need for additional lipid lowering.
Objectives: Primary: to assess the 12-week efficacy of bempedoic acid 180 mg versus placebo in decreasing LDL-C in high CV risk patients with hyperlipidemia (with atherosclerotic cardiovascular disease [ASCVD] and/or underlying heterozygous familial hypercholesterolemia [HeFH]) who are not adequately controlled with their maximally tolerated lipid-modifying therapy, defined as maximally-tolerated statin therapy with and without other LMT.

Secondary:

- To evaluate the effect of 24-week treatment with bempedoic acid 180 mg versus placebo on LDL-C
- To evaluate the effect of bempedoic acid 180 mg versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), high-sensitivity C reactive protein (hsCRP), and apolipoprotein B (apo B) after 12 weeks of treatment.

Tertiary objectives are included in the main body of the report (Section 8.1.3).

Methodology: This was a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and long-term of bempedoic acid in patients with ASCVD and/or HeFH who were at high risk for a CV event and who had elevated LDL-C, despite stable treatment with maximally tolerated statin therapy with or without other LMTs. Maximally tolerated lipid-modifying therapy included a maximally tolerated statin alone or in combination with other LMTs (eg, ezetimibe, fibrates [except gemfibrozil], and proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors). Maximally tolerated statin included statin regimens other than daily dosing, including no to very low doses, but reasons for not using high-intensity statin dosing must have been documented. A patient's maximally tolerated lipid-modifying therapy was determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of LMT.

Screening Period

Screening (Visit S1) occurred approximately 5 weeks prior to randomization but could be extended for an additional 4 weeks if needed to adjust background medical therapy or for other reasons as specified in the protocol. Eligible patients returned to the clinical site at Week -4 (Visit S2) to initiate administration of single-blind (patient only) placebo. During this time, patients were to maintain their LMT, lipid lowering diet, and routine exercise program.

52-Week Double-Blind Treatment Period

On Day 1, eligible patients were randomized 2:1 to receive either bempedoic acid 180 mg or placebo once daily (QD) for 52 weeks. Randomization was stratified based on the patient's CV risk (ASCVD alone; HeFH with or without ASCVD) and baseline statin intensity (high intensity statin; moderate intensity statin; low intensity statin), for a total of 6 strata.

Randomized patients returned for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (T7). A phone visit occurred at Week 8 (Visit T3) and Week 36 (T6). Patients who discontinued IMP treatment were asked to continue to be followed for safety using the protocol-specified visit schedule and procedures. For details of study assessments, see the Schedule of Events in Appendix 1 of the protocol.

An independent expert Data Monitoring Committee (DMC) formally reviewed accumulating unblinded safety and efficacy data from this and other ongoing studies of bempedoic acid. A blinded independent expert Clinical Events Committee (CEC) adjudicated designated clinical CV endpoints.

Number of Patients Planned: 750

Number of Patients Analyzed: 779 patients for efficacy and safety (522 bempedoic acid, 257placebo); 493 bempedoic acid patients for pharmacokinetic (PK) analysis

Diagnosis and Main Criteria for Inclusion: Adult men and women (age ≥18 years or legal age of majority based on regional law, whichever was greater) who signed the informed consent document, had a fasting calculated LDL-C ≥100 mg/dL at Visit S1 (Week -5) and LDL-C ≥70 mg/dL at Visit S3 (Week-1), had a high CV risk defined as either a diagnosis of HeFH and/or having ASCVD (with established coronary heart disease [CHD] or CHD risk equivalents), and were on stable LMT, including maximally tolerated statin therapy.

At Visit S1, patients could not have any recent history (within 3 months prior to Visit S1 or between Visit S1 and randomization) of myocardial infarction, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of Visit S1), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, transient ischemic attack, endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization); total fasting TGs ≥500 mg/dL; glycated hemoglobin A_{1C} (HbA_{1C}) ≥10%; liver disease or dysfunction; renal dysfunction or nephritic syndrome or a history of nephritis including estimated glomerular filtration rate (eGFR) (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2); hematologic or coagulation disorders or a hemoglobin level <10.0 g/dL; or unexplained creatine kinase (CK) >3 × upper limit of normal (ULN) at any time prior to randomization. The complete list of eligibility criteria is provided in Protocol Section 7.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number: During the double-blind treatment period, bempedoic acid was supplied as 180 mg, film-coated tablets in 35- and/or 100-count (depending on study visit) bottles. The matching placebo was a tablet of identical physical appearance and packaging. IMP was administered by mouth QD with or without food. Lot numbers are provided in Appendix 16.1.6.

Duration of Treatment: Patients were followed in this study for approximately 5 weeks for screening and 52 weeks of double-blind treatment.

Study Endpoints:

Efficacy

The primary efficacy endpoint was the percent change from baseline to Week 12 in LDL-C. Baseline LDL-C was defined as the mean of the LDL-C values from Week -1 and predose Day 1/Week 0 (last 2 non-missing values on or prior to Day 1).

Secondary endpoints included:

- Percent change from baseline to Week 24 in LDL-C
- Percent change from baseline to Week 12 in non-HDL-C, TC, apo B, and hsCRP
- Absolute change from baseline to Weeks 12 and 24 in LDL-C

Safety

Safety endpoints were:

- Patient incidence of treatment-emergent adverse events
- Safety laboratory values and vital signs
- Adjudicated cardiovascular event rates

Statistical Methods:

The following populations were defined for analysis purposes:

- The Full Analysis Set (FAS), also known as the intention-to-treat set, included all randomized patients. The FAS was used for all efficacy analyses and summaries for disposition, demographics, and baseline characteristics. Patients in the FAS were included in their randomized treatment group regardless of actual treatment.
- The Safety Analysis Set included all randomized patients who received at least 1 dose of IMP. The Safety Analysis Set was used for demographics and baseline characteristics, treatment exposure, concomitant medications, and all safety summaries. Patients in the Safety Analysis Set were included in the treatment group that they received, regardless of their randomized treatment.
- The PK Analysis Set included all patients in the Safety Analysis Set who had at least 1 non-missing PK assessment. These patients were evaluated for PK concentration summaries unless major protocol deviations were identified that could have affected the data or if key dosing or sampling information was missing.

Efficacy Analyses:

The primary and secondary endpoints were tested sequentially in the order below in a step-down testing procedure to control overall type I error. Each endpoint was tested at an alpha level of 0.05 and tested only if the previous endpoint achieved statistical significance.

1. Percent change from baseline to Week 12 in LDL-C (primary endpoint)
2. Percent change from baseline to Week 24 in LDL-C
3. Percent change from baseline to Week 12 in non-HDL-C
4. Percent change from baseline to Week 12 in TC
5. Percent change from baseline to Week 12 in apo B
6. Percent change from baseline to Week 12 in hsCRP

Efficacy data (actual value, change and percent change from baseline) from all visits was summarized using descriptive statistics with both conventional and standard units. Baseline for LDL-C, HDL-C, non-HDL-C, TG, and TC were defined as the mean of the lipid values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). If a repeat lipid measurement was performed at Week -1 (Visit S3), then baseline was the mean of the lipid values from the second Week -1 assessment and predose Day 1/Week 0 (Visit T1). Baseline for apo B and hsCRP was defined as the predose Day 1/Week 0 (Visit T1) value.

Percent change in LDL-C, non-HDL-C, TC, and apo B were analyzed using an analysis of covariance (ANCOVA) model, with treatment and randomization strata (patient's CV risk and baseline statin dose) as factors, and respective baseline values as a covariate. Missing data for efficacy endpoints was imputed using a pattern-mixture model as described in SAP Section 17. The ANCOVA output included the least square (LS) mean and standard error (SE) for each treatment group, along with the placebo-correct LS mean and its 95% CI and p value. For hsCRP, a non-parametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and CI was performed.

Sensitivity analyses of the primary efficacy endpoint included an on-treatment analysis and analyses using observed data only, derived randomization strata instead of the strata recorded by the interactive

web response system, and excluding patients who initiated additional LMT prior to the change of the post-baseline LMT.

Safety Analyses:

Safety endpoints for this study included adverse events (including pre-specified adverse events of special interest [AESIs] and adjudicated CV endpoints), clinical safety laboratories, physical examination findings, vital signs, and ECGs. All adverse events were coded by system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Affairs (MedDRA) Version 20.1. The summarization of adverse events included only treatment-emergent adverse events (TEAEs), defined as adverse events that began or worsened after randomization and the first dose of IMP and up to 30 days after the last dose date of IMP. Clinical CV endpoints were adjudicated by an independent blinded expert clinical event committee using standardized definitions. Descriptive summaries were produced for all safety endpoints.

RESULTS:

Patient Disposition:

Screened: 2300 patients

Randomized: 779 patients (522 bempedoic acid, 257 placebo)

Discontinued IMP: 107 (20.5%) bempedoic acid, 43 (16.7%) placebo

Withdrew from study: 32 (6.1%) bempedoic acid, 7 (2.7%) placebo

Demographic and Baseline Characteristics:

Sex: 496 (63.7%) men, 283 (36.3%) women

Mean (SD) age: 64.3 (8.79) years

Race: 735 (94.4%) White, 36 (4.6%) Black or African American, 4 (0.5%) Asian, 2 (0.3%) multiple, 1 (0.1%) American Indian or Alaska Native, 1 (0.1%) Native Hawaiian or Other Pacific Islander

Ethnicity: 717 (92.0%) not Hispanic or Latino; 62 (8.0%) Hispanic or Latino

Mean (SD) LDL-C: 120.43 (37.931) mg/dL

Efficacy Results: In patients on maximally tolerated statins with or without other LMTs, treatment with bempedoic acid 180 mg QD resulted in significantly greater reductions in LDL C (-15.07% LS mean percent change from baseline) compared with placebo (2.35%). The difference from placebo in LS means (-17.42%) was statistically significant ($p < 0.001$). Absolute mean changes from baseline to Week 12 in LDL-C were -21.2 and 0.0 mg/dL in the bempedoic acid and placebo groups, respectively (observed data only). Based on an on-treatment analysis that included only data collected during the treatment period (ie, up to the date of last IMP dose + 7 days), treatment with bempedoic acid resulted in a difference from placebo in LS means of -18.36% ($p < 0.001$). Differences from placebo for bempedoic acid in LDL-C reductions were also significant for the secondary endpoint at Week 24 ($p < 0.001$), were durable over 52 weeks, and did not vary by the intensity of background statin therapy or a range of baseline subgroups. Bempedoic acid also demonstrated significant treatment effects compared with placebo based on secondary endpoints at Week 12 for non-HDL-C ($p < 0.001$), TC ($p < 0.001$), apo B ($p < 0.001$), and hsCRP ($p = 0.039$). In the on-treatment analyses, there were greater reductions with bempedoic acid in LDL-C at Week 24, and in non-HDL-C, TC, apo B, and hsCRP at Week 12, all compared with placebo ($p < 0.001$ for LDL-C, non-HDL-C, TC, and apo B endpoints; $p = 0.024$ for hsCRP).

Primary and secondary efficacy analyses in the FAS based on the percent change from baseline are summarized below:

Parameter % Change from Baseline	Placebo (N = 257)	Bempedoic Acid (N = 522)	Difference (Bempedoic Acid vs Placebo)		
			LS Means (SE)	95% CI	P value
LDL-C at Week 12, n	257	522	-	-	-
LS mean (SE)	2.35 (1.446)	-15.07 (1.073)	-17.42 (1.800)	-20.951, -13.896	<0.001
LDL-C at Week 24, n	247	485	-	-	-
LS mean (SE)	2.66 (1.910)	-12.10 (1.479)	-14.77 (2.418)	-19.504, -10.027	<0.001
Non-HDL-C at Week 12, n	253	498	-	-	-
LS mean (SE)	2.28 (1.351)	-10.75 (0.952)	-13.03 (1.652)	-16.270, -9.794	<0.001
TC at Week 12, n	253	499	-	-	-
LS mean (SE)	1.26 (1.010)	-9.94 (0.688)	-11.20 (1.224)	-13.599, -8.801	<0.001
apo B at Week 12, n	245	479	-	-	-
LS mean (SE)	3.73 (1.340)	-9.29 (0.851)	-13.02 (1.587)	-16.130, -9.907	<0.001
hsCRP at Week 12, n	240	467	-	-	-
Median (IQR)	-9.366 (71.561)	-18.699 (69.931)	-8.733[a]	-17.238, -0.434	0.039

apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; LS = least square; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol

Note: Percent change from baseline for LDL-C, non-HDL-C, TC and apo B was analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (HeFH vs. ASCVD, and high intensity statin vs. other statin) as factors and baseline lipid parameter as a covariate. For LDL-C, non-HDL-C and TC, baseline was defined as the mean of the values at screening and predose Day 1/Week 0 (Visit T1); for apo B and hsCRP, baseline was defined as the last value prior to first dose of IMP. Missing data for LDL-C, non-HDL-C, TC and apo B were imputed through multiple imputation using a pattern mixture model (PMM) accounting for treatment adherence. Analysis for hsCRP was based on Wilcoxon rank sum test and Hodges-Lehmann estimates for location shift and CI; median (IQR) was presented within each treatment group.
The Full Analysis Set (FAS) consisted of all randomized patients.
[a] Location shift

Safety Results: Bempedoic acid was safe and well-tolerated in this long-term study in patients with ASCVD and/or HeFH and who had elevated LDL-C despite treatment with maximally tolerated statins with and without other LMTs with a safety profile similar to that observed for placebo.

- Most patients had ≥1 treatment-emergent adverse event with similar frequencies across the treatment groups (70.1% bempedoic acid, 70.8% placebo). The most frequently reported adverse event overall by preferred term was nasopharyngitis (5.2% bempedoic acid, 5.1% placebo). Overall, the frequencies of the most common (≥2% of patients in either group) preferred term events were balanced across the treatment groups, with no notable increases in the bempedoic acid group.
- Similar percentages of patients across the treatment groups experienced ≥1 of the following: serious adverse events (20.3% bempedoic acid, 18.7% placebo) and IMP-related serious adverse events (0.4% bempedoic acid, 0.4% placebo).
- Adverse events were evenly distributed across the groups by severity: mild (21.5% bempedoic acid, 19.8% placebo), moderate (33.1% bempedoic acid, 36.6% placebo), and severe (15.5% bempedoic acid, 14.4% placebo).
- A total of 8 patients (6 [1.1%] bempedoic acid and 2 [0.8%] placebo) had adverse events with a fatal outcome within 30 days of the last dose of IMP. Of these, 4 patients (0.8%) in the

bempedoic acid group and 2 patients (0.8%) in the placebo group had adverse events with a fatal outcome that were adjudicated as CV death. For the other 2 patients in the bempedoic acid group, the adverse events with fatal outcome included gas poisoning and septic shock that began during a pre-scheduled surgical procedure. All deaths were determined to be unlikely related or not related to IMP by the investigator. The rate and types of fatal events was consistent with expectations relative to the very high-risk patient population and other studies of similar trial design.

- Adverse events leading to discontinuation of IMP occurred in 10.9% and 8.6% of patients in the bempedoic acid and placebo groups, respectively. The difference in frequency was not driven by any single SOC or preferred term, and no preferred term occurred in >1% of patients in either group. Myalgia was the most common adverse event leading to discontinuation of IMP in both groups (1.0% bempedoic acid, 0.8% placebo).
- AESIs were evaluated based on predefined adverse event preferred terms and, when appropriate, additional adverse event and laboratory data. Results by AESI category included:
    - Hepatic events: adverse events in this AESI category occurred in 2.7% of bempedoic acid patients and 1.6% of placebo patients. By preferred term, only alanine aminotransferase (ALT) increase occurred with a ≥1% difference between groups (1.1% bempedoic acid, 0% placebo). No events in this AESI category were considered serious adverse events. Six patients (5 bempedoic acid, 1 placebo) had AESIs in this category that led to discontinuation of IMP and included the following preferred terms: included alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, and liver function test increased. Of these, 3 bempedoic acid patients and 1 placebo patient had repeated and confirmed elevations in AST and/or ALT >3 × ULN and all had values returned to within normal limits by the end of the study. Repeat and confirmed increases in ALT or aspartate aminotransferase (AST) >3 × ULN occurred in 6 bempedoic acid patients (1.1%) and 2 placebo patients (0.8%). Of these, 1 (0.2%) bempedoic acid patient and 1 (0.4%) placebo patient had repeat and confirmed increases in AST or ALT >5 × ULN. No patient in either treatment group had total bilirubin >2 × ULN or met the criteria for potential Hy's Law.
    - Muscular safety events: adverse events in the AESI category of Muscular disorders occurred in 7.5% of bempedoic acid patients and 5.1% in placebo patients; by preferred term, pain in extremity (2.1% bempedoic acid, 0.4% placebo) was the only event that occurred with ≥1% difference between groups. Myalgia (2.9% bempedoic acid, 3.1% placebo) and muscular weakness (0.4% bempedoic acid, 0.4% placebo) occurred at similar frequencies in both groups. AESIs in the CK elevations category occurred in 0.8% of bempedoic acid patients and 1.2% of placebo patients. No events in this AESI categories of muscular disorders and CK elevations were considered serious adverse events. Eleven patients (9 bempedoic acid, 2 placebo) had adverse events that led to discontinuation of IMP in the category of muscular disorders. Preferred terms included myalgia, pain in extremity, and muscle spasms; all resolved by the end-of-study. One patient in the bempedoic acid group had an adverse event that led to discontinuation to IMP in the category of CK elevations. Based on laboratory data, repeat and confirmed postbaseline CK values >5 × ULN occurred in

no patients in the bempedoic acid group and 1 patient (0.4%) in the placebo group. No patients in either group had values >10 × ULN.

- Metabolic acidosis: no adverse events in this AESI category were reported in either group.
- Hypoglycemia: adverse events in this AESI category occurred in 1.3% of bempedoic acid patients and 0.8% of placebo patients.
- New onset or worsening of diabetes: adverse events in this AESI category occurred in 6.9% of bempedoic acid patients and 7.4% of placebo patients. Most events were reported at a higher frequency in the placebo group compared with bempedoic acid. No patients had serious adverse events in this AESI category. One patient in the placebo group had an adverse event in this AESI category that led to discontinuation of IMP. Based on laboratory results, Mean HbA1c changes from baseline to Week 12 and 52 in patients with diabetes at baseline were small overall: -0.08% and 0.17% in bempedoic acid patients and 0.13% and 0.26% in placebo patients, respectively. For patients with no history of diabetes at baseline, changes were similar (-0.04% and 0.05% for bempedoic acid and -0.01% and 0.03% for placebo).
- Renal events: bempedoic acid treatment resulted in small increases from baseline of 0.052 to 0.056 mg/dL through Week 52 compared with mean changes from baseline of -0.001 to 0.012 mg/dL in the placebo group. These changes were associated with decreases in eGFR (based on MDRD calculated from creatinine). Two patients (0.4%) in the bempedoic acid group and no patients in the placebo group had eGFR <15 mL/min/1.73 m^2 at any postbaseline visit. eGFR values of 15 to <30 mL/min/1.73 m^2 occurred in 9 patients (1.7%) and 3 patients (1.2%) in the bempedoic acid and placebo groups, respectively, at any postbaseline visit. Adverse events in this AESI category occurred in 3.3% of bempedoic acid patients and 1.9% of placebo patients. Two bempedoic acid patients and 1 placebo patient had adverse events of acute kidney injury. Of these, 1 was considered a serious adverse event. No other events in this AESI category were considered serious adverse events. Two patients in the bempedoic acid group had adverse events with a preferred term of renal failure. Both were considered mild in intensity by the investigator and neither was considered a serious adverse event or led to discontinuation of IMP. Neither patient had an eGFR value below 30 mL/min/1.73 m^2 at any study visit. One bempedoic acid patient had an adverse event of glomerular filtration rate decreased that led to discontinuation of IMP. One placebo patient had an adverse event of renal impairment that led to discontinuation of IMP. No other events in this AESI category led to discontinuation of IMP.
- CV events: any positively-adjudicated CV endpoint occurred in 8.2% of bempedoic acid patients and 10.1% of placebo patients; the difference was driven by a lower patient incidence in non-fatal myocardial infarction (1.0% bempedoic acid, 2.7% placebo), coronary revascularization (3.8% vs 5.8%), and non-coronary arterial revascularization (1.1% vs 2.3%). In a post hoc analysis, lower percentages of patients in the bempedoic acid group had 3-component MACE (2.7%), 4-component MACE (5.7%), and 5-component MACE (6.1%) compared with placebo (4.7%, 7.8%, and 8.2%, respectively).

- Neurocognitive/neurologic events: adverse events in this AESI category were similar between groups (0.6% bempedoic acid, 0.4% placebo). One patient in the placebo group had an adverse event of amnesia that led to discontinuation of IMP.
- Increased uric acid: Mean serum uric acid increased postbaseline in the bempedoic acid group, with mean changes of 0.73 to 0.85 mg/dL (13.6% to 15.5% increase from baseline) compared with mean changes of -0.06 to 0.04 mg/dL (-0.22% to 1.4% change from baseline) in the placebo group over 52 weeks. This increase was seen by Week 4 and remained stable through Week 52. Adverse events of gout occurred in 11 patients (2.1%) in the bempedoic acid group compared with 2 patients (0.8%) in the placebo group. Among the 11 patients in the bempedoic acid group, 5 patients had a history of gout and 3 patients had a history of hyperuricemia. One of 2 placebo patients with adverse events of gout had a medical history of gout. Uric acid values at baseline in patients with adverse events of gout were above the ULN in 10 of 11 bempedoic acid patients and 1 of 2 placebo patients. Adverse events of blood uric acid increased and hyperuricemia occurred in 14 patients (2.7%) and 22 patients (4.2%) in the bempedoic acid group, respectively, and 1 patient (0.4%) and 5 patients (1.9%) in the placebo group, respectively. No events in this AESI category were considered serious adverse events. One bempedoic acid patient had an adverse event of blood uric acid increased that led to discontinuation of IMP. For most patients, these events were mild to moderate in severity and managed without interruption or discontinuation of treatment with bempedoic acid.
- Decreased hemoglobin: bempedoic acid treatment resulted in small mean decreases in hemoglobin that began within the first 4 weeks of treatment and were stable over 52 weeks compared with placebo. Decreases ≥2 g/dL from baseline occurred in 3.8% of patients in the bempedoic acid group compared with 1.6% in the placebo group. Hemoglobin values <8 g/dL were not reported for any patient in either group. Adverse events of anemia or hemoglobin decreased occurred in 2.7% and 0.2%, respectively, of bempedoic acid patients and 1.2% and 0%, respectively, of placebo patients.

- There were no treatment-related changes in other laboratory parameters or vital signs and no clinically significant abnormal shifts in ECGs measurements from baseline to end-of-study.

CONCLUSIONS:

Results from this 52-week, Phase 3, randomized (2:1), double-blind, placebo-controlled study of bempedoic acid 180 mg QD in 779 patients with hyperlipidemia at high risk for CV events who had elevated LDL-C despite treatment with maximally-tolerated statin therapy with and without other LMTs demonstrated the following:

- In patients on maximally tolerated statins with or without other LMTs, treatment with bempedoic acid resulted in statistically significant reductions in LDL-C at Week 12 compared with placebo of (LS means difference from placebo of 17.42%; p <0.001). The LS mean percent changes from baseline were -15.07% for bempedoic acid compared with 2.35% for placebo. Absolute mean changes from baseline to Week 12 in LDL-C were -21.2 and 0.0 mg/dL in the bempedoic acid and placebo groups, respectively (observed data only).
- Based on an on-treatment analysis of the primary efficacy endpoint that included only data collected during the treatment period (ie, data collected up to the date of last IMP dose

+ 7 days), treatment with bempedoic acid resulted in a difference from placebo at Week 12 in LS means of -18.36% ($p < 0.001$).

- The overall treatment benefit of bempedoic acid was also observed across all secondary endpoints ($p < 0.001$ for LDL-C at Week 24; $p < 0.001$ for apo B, non-HDL-C, and TC at Week 12; $p = 0.039$ for hsCRP at Week 12). The LS mean difference between bempedoic acid and placebo in percent change from baseline was -14.77% for LDL-C at Week 24, and -13.03% for non-HDL-C, -11.20% for TC, and -13.02% for apo B at Week 12. The median percent change in hsCRP was -18.70% for bempedoic acid and -9.37% for placebo resulting in a location shift in hsCRP of -8.733% at Week 12. The on-treatment analyses were consistent with results of the secondary endpoint analyses ($p < 0.001$ for LDL-C, apo B, non-HDL-C, and TC endpoints; $p = 0.024$ for hsCRP).
- LDL-C reductions were sustained over 52 weeks and did not vary by the intensity of background statin therapy (ie, high baseline statin intensity vs low/moderate statin intensity) or a range of baseline subgroups.
- Bempedoic acid treatment was well-tolerated with a similar safety profile to placebo. Adverse events with bempedoic acid were generally similar to those with placebo, including the patient incidence and severity of any adverse event, serious adverse event, positively-adjudicated CV clinical events, and AESIs in the metabolic acidosis, hypoglycemia, and neurocognitive/neurologic categories.
- The patient incidence of fatal adverse events and adverse events leading to discontinuation of IMP was low with bempedoic acid. None of the fatal adverse events were considered related to IMP by the investigator or the Sponsor. Of the 8 patients overall with adverse events with a fatal outcome within 30 days of the last dose of IMP, 4 patients (0.8%) in the bempedoic acid group and 2 patients (0.8%) in the placebo group had adverse events with a fatal outcome that were adjudicated as CV death. For the other 2 patients in the bempedoic acid group, the adverse events with fatal outcome included gas poisoning and septic shock that resulted from a pre-scheduled surgical procedure. Medical review of individual cases did not reveal any safety concern associated with bempedoic acid treatment for fatal adverse events or adverse events leading to discontinuation of IMP. The rate and types of fatal events was consistent with expectations relative to the very high risk and older patient population and other clinical trials with a similar trial design.
- The patient incidence of any positively-adjudicated clinical endpoint was lower in the bempedoic acid group (8.2%) compared with placebo (10.1%). In a post hoc analysis, lower percentages of patients in the bempedoic acid group had 3-component MACE (2.7%), 4-component MACE (5.7%), and 5-component MACE (6.1%) compared with placebo (4.7%, 7.8%, and 8.2%, respectively).
- The patient incidence of repeated and confirmed AST and/or ALT > 3 × ULN and Hepatic Disorders AESIs were low overall and occurred in 1.1% and 0.8%, respectively, of bempedoic acid patients and placebo patients, and in 2.7% and 1.6% of patients, respectively.
- The patient incidence of CK elevations (based on adverse events and repeated and confirmed CK > 5 × ULN), adverse events of muscular weakness and myalgia, and discontinuations due to muscle-related adverse events were low with bempedoic acid and similar to that with placebo.

- The patient incidence of new onset or worsening diabetes adverse events was 6.9% in the bempedoic acid group and 7.4% in the placebo group. Mean HbA1c changes from baseline to Week 12 and 52 in patients with diabetes at baseline were smaller in patients in the bempedoic acid group (-0.08% and 0.17%) compared with patients in the placebo group (0.13% and 0.26%).
- Bempedoic acid treatment resulted in small mean increases in uric acid that were consistent over 52 weeks. A higher percentage of patients in the bempedoic acid group had adverse events of gout, blood uric acid increased, and hyperuricemia (2.1%, 2.7%, and 4.2%, respectively) compared with placebo (0.8%, 0.4%, and 1.9%, respectively). Most patients with these events had a prior history of gout and/or baseline uric acid levels that were above the ULN. In general, these events were mild to moderate in severity and managed without interruption or discontinuation of treatment with bempedoic acid.
- Bempedoic acid treatment resulted in small increases in serum creatinine associated with small decreases in eGFR. The patient incidence of adverse events related to eGFR was low overall, but numerically higher with bempedoic acid compared with placebo.
- Bempedoic acid treatment resulted in small mean decreases in hemoglobin that were durable over 52 weeks compared with placebo, with a higher percentage of patients in the bempedoic acid group (3.8%) having decreases of ≥2 g/dL from baseline compared with placebo (1.6%); 5 bempedoic acid patients and 1 placebo patient had decreases in hemoglobin >3 g/dL from baseline. Adverse events of anemia occurred in 2.7% of bempedoic acid patients and 1.2% of placebo patients.

Date and Version of the Report:

07 January 2019

Source: Applicant

15.3. Trial 046

Title of Study: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C who are Statin Intolerant (1002-046) (ClinicalTrials.gov No. NCT02988115)
Indication: (b) (4)
Investigational Product: Bempedoic acid
Name of Sponsor: Esperion Therapeutics, Inc.
Publications: none
Investigators and Study Sites: This study was conducted at 67 study sites in North America, of which 64 sites randomized patients. Study sites and investigators are listed in Appendix 16.1.4.
Phase of Development: 3
Study Period: Date first subject screened: 16 Nov 2016 Date last subject completed: 16 Mar 2018
Background and Rationale for the Study: Cardiovascular disease (CVD) remains the leading cause of death among Americans, Europeans, and other populations around the world (WHO, 2015). An increasing body of evidence suggests that the absolute amount of low-density lipoprotein cholesterol (LDL-C) lowering is proportional to CVD risk reduction by statin and nonstatin therapies that lower LDL-C via upregulation of LDL receptors (Silverman et al, 2016; Cholesterol Treatment Trialists' Collaboration, 2010; Ference et al, 2017). The approval of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, was one of the most important advances in the management of CVD risk, decreasing risk of cardiovascular (CV) morbidity and mortality by approximately 25% in eligible patients (Cholesterol Treatment Trialists' Collaboration, 2010). However, as many as 10% of patients are unable to tolerate statins at any dose and some patients are unable to tolerate statins due to dose-limiting toxicities and side effects that result in intolerance and/or contraindications (Thompson et al, 2016; Jacobson et al, 2014). Muscle-related complaints, which encompass a range of conditions from myalgia to rare but life- threatening rhabdomyolysis, represent a major cause of statin discontinuation in clinical practice (Joy and Hegele, 2009). Like statins, bempedoic acid decreases liver cholesterol synthesis, which results in increased LDL receptor activity and LDL particle clearance from the blood. ETC-1002-CoA (via adenosine triphosphate-citrate lyase [ACL] inhibition) and statins (via HMG-CoA reductase inhibition) both inhibit cholesterol synthesis in the liver; however, bempedoic acid is a prodrug that requires coenzyme A (CoA) activation by hepatic activation by very long-chain acyl-CoA synthetase 1 (ACSVL1); thus, bempedoic acid is inactive in skeletal muscle. This 24-week Phase 3 study was designed to assess the efficacy, safety and tolerability of bempedoic acid vs placebo in patients with elevated LDL-C who demonstrated the inability to tolerate 2 statins including one at a low dose and whose highest tolerated dose of statin (if any) was less than the lowest approved dose of a statin.

Objectives:

Primary:

- To assess the 12-week efficacy of bempedoic acid 180 mg/day vs placebo in decreasing LDL-C in patients with elevated LDL-C who are statin intolerant.

Secondary:

- To evaluate the effect of 24-week treatment with bempedoic acid 180 mg/day vs placebo on LDL-C
- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day vs placebo on
  - non-high-density lipoprotein cholesterol (non-HDL-C)
  - total cholesterol (TC)
  - high-sensitivity C-reactive protein (hsCRP)
  - apolipoprotein B (apo B)
- To evaluate the 24-week safety and tolerability of bempedoic acid 180 mg/day compared with placebo.

Tertiary objectives are included in the main body of the report (Section 8.1.3).

Methodology: This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study. The study consisted of an approximately 1-week screening period, a 4-week single-blind placebo run-in period, and a 24-week treatment period.

Screening Period

Patients started screening at Week -5 (Visit S1), approximately 5 weeks prior to randomization. The 1-week screening could have been extended for an additional 4 weeks if needed, to adjust background medical therapy or for other reasons, as specified in the Protocol (Appendix 16.1.1). Eligible patients returned to the clinical site at Week -4 (Visit S2) to begin treatment with single-blind placebo.

Patients who met all enrollment criteria continued their allowed stable background lipid-modifying therapy (LMT) and maintained consistent diet and exercise patterns throughout the study.

Placebo Run-in Period

Eligible patients began the single-blind, placebo run-in period at Week -4 (Visit S2). Patients were assessed to determine if they still met all enrollment criteria. At Week -1, patients returned for Visit S3, for continued determination of enrollment criteria. With implementation of Protocol Amendment 1, patients were required to have fasting LDL-C $\geq$70 mg/dL (1.8 mmol/L) at Week -1 (Visit S3) to continue to be eligible for the study.

Treatment Period

Patients were stratified by primary prevention vs secondary prevention and/or heterozygous familial hypercholesterolemia (HeFH) and randomized 2:1 on Day 1 to receive either bempedoic acid or placebo once daily (QD) for 24 weeks. Randomized patients returned for clinic visits at Weeks 4, 12, and 24. A phone visit occurred at Week 8.

Number of Patients (Planned and Analyzed):

Planned: 300

Analyzed: 345 patients randomized and treated

Diagnosis and Main Criteria for Inclusion: Adult men and women (age ≥18 years or legal age of majority based on regional law, whichever was greater) who signed the written informed consent document, met criteria for primary or secondary CV prevention, had elevated LDL-C, and were statin intolerant. Statin intolerance was defined as an inability to tolerate 2 or more statins, one at a low dose, due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued. Patients who were tolerating stable, very low dose statin therapy (less than the lowest approved starting dose) could continue therapy throughout the study. Primary prevention patients must have had at minimum a history of requiring LMT based on local guidelines with a LDL-C of ≥130 mg/dL (3.4 mmol/L) and patients with secondary prevention included coronary artery disease, symptomatic peripheral artery disease, and/or cerebrovascular atherosclerotic disease; and/or HeFH as defined in the protocol with a LDL-C of ≥100 mg/dL (2.6 mmol/L) at Week -5 (Visit S1). All patients had to have had fasting LDL-C ≥70 mg/dL (1.8 mmol/L) at Week -1 (Visit S3). Patients could not have any recent history of myocardial infarction, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, transient ischemic attack, endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization); total fasting triglycerides (TG) ≥500 mg/dL (5.6 mmol/L) at Week -5 (Visit S1); hemoglobin A_{1C} (HbA_{1C}) ≥10% at Week -5 (Visit S1); liver disease or dysfunction; renal dysfunction or glomerulonephropathy; hematologic or coagulation disorders or a hemoglobin level <10.0 g/dL at Week -5 (Visit S1); or unexplained creatine kinase >3 × upper limit of normal at any time prior to randomization. The complete list of eligibility criteria is provided in Protocol Section 6.
Investigational Product, Non-investigational Product, Dose and Mode of Administration, Lot Number: During the double-blind treatment period, bempedoic acid was supplied as 180 mg, film-coated tablets in 100-count bottles. The matching placebo was a tablet of identical physical appearance and packaging. Placebo was supplied in 35-count bottles for the single-blind placebo run-in period only. Investigational medicinal product (IMP) was administered by mouth, QD with or without food. Lot numbers are provided in Appendix 16.1.6.
Duration of Treatment: Duration of the study for an individual patient was up to approximately 29 weeks (1 week for screening, 4 weeks for single-blind placebo run-in, and 24 weeks of treatment with double-blind IMP).

Study Endpoints:

Efficacy

The primary efficacy endpoint was the percent change from baseline to Week 12 in LDL-C. Baseline LDL-C was defined as the mean of the LDL-C values from Week -1 and predose Day 1/Week 0 (last two non-missing values on or prior to Day 1).

The key secondary efficacy endpoints included in the hierarchical analysis were percent change from baseline to Week 24 in LDL-C and percent change from baseline to Week 12 in non-HDL-C, TC, apo B, and hsCRP. Other secondary efficacy endpoints were the absolute change from baseline in LDL-C at Weeks 12 and 24.

Tertiary endpoints are included in the main body of the report (Section 8.2.3).

Safety

Safety endpoints were:

- patient incidence of treatment-emergent adverse events (including adverse events of special interest [AESI])
- safety laboratory values and vital signs
- CV event rates

Statistical Methods:

Patient populations were defined for analysis as follows:

- Full Analysis Set (FAS) was used for all efficacy analyses and was defined as all randomized patients.
- Completer Analysis Set, used for all the primary and secondary efficacy, was defined as all patients in the FAS who completed IMP per the end of treatment CRF page and had non-missing Week 12 LDL-C values.
- Safety Analysis Set, used for all safety summaries, was defined as all randomized patients who received at least 1 dose of IMP.
- Pharmacokinetic (PK) Analysis Set included all patients in the Safety Analysis Set who had at least one non-missing PK assessment.

Primary Efficacy Analysis

The primary efficacy endpoint was analyzed using analysis of covariance (ANCOVA), with treatment group and stratification factor patient type as factors and baseline LDL-C as a covariate. The ANCOVA was performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they received. Descriptive statistics were summarized for LDL-C at each visit and for change from baseline.

Secondary Efficacy Analyses

Key secondary endpoints of LDL-C, non-HDL-C, TC, and apo B were analyzed using the ANCOVA model described previously. For hsCRP, non-parametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and confidence interval was performed. Other secondary efficacy endpoints were summarized with descriptive statistics.

Pharmacokinetic Analyses

Descriptive statistics for plasma concentrations of bempedoic acid (ETC-1002) and its metabolite (ESP15228) were summarized for Visits T2, T4, and T5 (Weeks 4, 12, and 24, respectively).

Safety Analyses

All outputs for safety outcomes were based on the Safety Analysis Set. No statistical comparisons were made between the treatment groups for safety data, unless otherwise specified within the relevant section.

Results:

Patient Disposition

Screened: 602 patients

Randomized: 345 patients (234 bempedoic acid, 111 placebo)

Discontinued IMP: 58 (24.8%) bempedoic acid, 18 (16.2%) placebo

Withdrew from study: 14 (6.0%) bempedoic acid, 4 (3.6%) placebo

Demographic and Baseline Characteristics

Sex: 151 (43.8%) men, 194 (56.2%) women

Mean (standard deviation [SD]) age: 65.2 (9.50) years

Race: 307 (89.0%) white, 26 (7.5%) black or African American, 8 (2.3%) Asian, 2 (0.6%) Native Hawaiian or other Pacific Islander, and 1 (0.3%) multiple

Ethnicity: 17 (4.9%) Hispanic or Latino; 328 (95.1%) not Hispanic or Latino

Cardiovascular risk category: 211 (61.2%) primary prevention; 134 (38.8%) secondary prevention

Mean LDL-C (standard deviation): 157.55 (39.854) mg/dL

Efficacy Results:

In the primary efficacy analysis, treatment with bempedoic acid resulted in significantly greater least squares (LS) mean reductions in percent change in LDL-C from baseline to Week 12 (-22.58%) compared with placebo (-1.17%) in high-risk patients with elevated LDL-C who were unable to tolerate a statin at the lowest approved starting dose. The LS mean placebo-corrected difference (-21.41%) was statistically significant (p <0.001). The secondary endpoint of LS mean difference from placebo in absolute LDL-C reduction from baseline (based on observed data) was -39.3 mg/dL at Week 12.

In the key secondary efficacy analyses, the LS mean differences between bempedoic acid and placebo in percent change from baseline were statistically significant (p <0.001 for all) at Week 24 for LDL-C (-18.91%), and at Week 12 for non-HDL-C (-17.94%), TC (-14.76%), and apo B (-14.96%). The location shift for hsCRP at Week 12 was -24.3%. The absolute change from baseline to Week 12 in LDL-C was -39.3 mg/dL in the bempedoic acid group and -3.1 mg/dL in placebo and at Week 24 was -37.0 mg/dL in the bempedoic acid group and -5.1 mg/dL in the placebo group. Tertiary endpoints are summarized in the main body of the report (Section 11.1.3).

Primary and secondary efficacy analyses in the FAS population based on the percent change from baseline are summarized below:

Parameter Percent Change From Baseline	Placebo (N = 111)	Bempedoic Acid (N = 234)	p-value
Primary Endpoint			
LDL-C (Week 12), n	107	224	
LS Means (SE)	-1.17 (1.421)	-22.58 (1.290)	<0.001
Secondary Endpoints			
LDL-C (Week 24), n	106	217	
LS Means (SE)	-2.26 (1.552)	-21.17 (1.411)	<0.001
Non-HDL-C (Week 12), n	107	224	
LS Means (SE)	-0.14 (1.169)	-18.08 (1.114)	<0.001
TC (Week 12), n	107	224	
LS Means (SE)	-0.61 (0.961)	-15.37 (0.879)	<0.001
apo B (Week 12), n	104	218	
LS Means (SE)	0.32 (1.177)	-14.65 (1.080)	<0.001
hsCRP (Week 12), n	103	218	
Location shift		-24.290	<0.001
Asymptomatic Confidence Limits (Confidence Interval Midpoint)		(-35.888, -12.712) (-24.300)	

ANCOVA = analysis of covariance; apo B = apolipoprotein B; CI = confidence interval; CVD = cardiovascular disease; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LS means = least squared means; non-HDL-C = non-high-density lipoprotein cholesterol; SE = standard error; TC = total cholesterol.

Baseline for LDL-C, non-HDL-C, and TC was defined as the mean from the last two non-missing values on or prior to Day 1. Baseline for apo B and hsCRP was defined as the last non-missing value on or prior to Day 1. LS means, 95% CIs and P-values are based on an ANCOVA with percent change from baseline as the dependent variable, treatment and CVD risk category (primary prevention; secondary prevention) as a fixed effects and baseline as a covariate. In the ANCOVA model, the missing parameter at Week 12 was imputed

using a multiple imputation method taking into account adherence to treatment. Patients who had missing value and were off treatment were imputed with placebo patients' data only. Percent change from baseline statistics (LS means and p-value) were based on the final combined estimators from Rubin's method. For hsCRP, the location shift and asymptomatic 95% CI and midpoint were based on Hodges-Lehman estimation.
Source: Table 14.2.2.1a, Table 14.2.2.3a, Table 14.2.2.4a, Table 14.2.2.5a, Table 14.2.2.6a

Pharmacokinetic Results:

Mean concentrations for ETC-1002 were 12161.94 ng/mL at Week 4, 11576.86 ng/mL at Week 12, and 11288.14 ng/mL at Week 24. Mean concentrations for ESP15228 were 1844.56 ng/mL at Week 4, 1720.03 ng/mL at Week 12, and 1721.51 ng/mL at Week 24.

Safety Results:

- A total of 150 patients (64.1%) in the bempedoic acid group and 63 patients (56.8%) in the placebo group had at least one treatment-emergent adverse event
- Fourteen patients (6.0%) in the bempedoic acid group and 4 patients (3.6%) in the placebo group had at least one serious adverse event. No serious AESIs occurred in the bempedoic acid group and 1 serious AESI (acute kidney injury) occurred in the placebo group. No IMP-related serious adverse events or deaths occurred during the study.
- Overall, 18.4% of patients in the bempedoic acid group and 11.7% in the placebo group had adverse events leading to discontinuation of IMP. Most adverse events that led to discontinuation of IMP occurred in 1 patient. There was no apparent trend in the type of adverse events leading to discontinuation of IMP and the difference in frequency was not driven by any single system organ class (SOC) or preferred term.
- Most adverse events were mild or moderate in intensity.
- Adverse events were assessed as IMP-related in 21.8% in bempedoic acid group and 18.0% in the placebo group.
- The incidence of AESIs including metabolic acidosis, hypoglycemia, and neurocognitive/neurologic events was low and similar between treatment groups. Pre-defined muscle-related adverse events occurred in 12.8% (n = 30) of patients receiving bempedoic acid and 16.2% (n = 18) who received placebo. New-onset or worsening of diabetes was 2.1% (n = 5) in the bempedoic acid treatment group compared with 4.5% (n = 5) in the placebo group.
- A positively adjudicated major adverse cardiac event (MACE) or non-MACE clinical endpoint occurred in 9 patients (3.8%) in the bempedoic acid group and 0 patients in the placebo group. All events occurred in patients with prior history of CVD (ie, secondary prevention) and were therefore at high risk for future CV events.
- Mean uric acid increased from baseline by 0.68 to 0.86 mg/dL in the bempedoic acid group and decreased by 0 to 0.12 mg/dL in the placebo group. Mean changes from baseline in creatinine in the bempedoic acid group were 0.057 mg/dL (Week 4), 0.054 mg/dL (Week 12) and 0.041 mg/dL (Week 24) compared with mean changes of -0.004 to 0.005 mg/dL for placebo. No hematology analytes had a >5% difference in the percentage of patients with shifts between treatment groups from normal at baseline to low or high during the study. Four patients in the bempedoic acid treatment group and no patient in the placebo group had an on study ALT and/or AST value that was >3 x ULN; 3 patients had repeated and confirmed values. No clinically meaningful changes were observed in other laboratory parameters, vital signs, physical examinations, or electrocardiogram findings

CONCLUSIONS:

Results from this 24-week, Phase 3, randomized, double-blind, placebo-controlled study of bempedoic acid 180 mg compared with placebo therapy (both added to background lipid-modifying therapy) in high-risk patients with elevated LDL-C who were statin intolerant demonstrate:

- Treatment with bempedoic acid 180 mg resulted in both clinically meaningful and statistically significant greater reductions in percent change in LDL-C at Week 12 (LS mean: -22.58% from baseline) compared with placebo (LS mean: -1.17%). The difference from placebo in LS means (-21.41%) was statistically significant ($p < 0.001$). Absolute mean change from baseline to Week 12 was -39.3 mg/dL in the bempedoic acid group. An on-treatment analysis that included only data collected during the treatment period (ie, up to the date of last IMP dose + 7 days), resulted in significantly greater reductions from baseline to Week 12 for LS mean percent change in LDL-C with bempedoic acid (-25.56%) compared with placebo (-1.67%); the difference in LS means was -23.88%, $p < 0.001$.
- The overall treatment benefit of bempedoic acid was also observed across all key secondary endpoints. The treatment difference between bempedoic acid and placebo in mean percent change from baseline at Week 24 was -18.91% for LDL-C and at Week 12 was -17.94%, -14.76%, and -14.96% for non-HDL-C, TC, and apo B, respectively ($p<0.001$ for each). The location shift for hsCRP from baseline to Week 12 was -24.3%.
- Bempedoic acid treatment was well-tolerated with a favorable safety profile compared with placebo. No deaths occurred during the study and no serious adverse events were deemed related to IMP. The patient incidence of adverse events and serious adverse events was similar between the bempedoic acid and placebo groups. Adverse events related to muscular disorders occurred in 12.8% of patients in the bempedoic acid group compared with 16.2% in the placebo group. The patient incidence of adverse events leading to discontinuation of IMP was 18.4% in the bempedoic acid group compared with 11.7% in the placebo group. When reviewing both SOCs and preferred terms, there were no meaningful differences between treatments in the adverse events that led to discontinuation of IMP. No new safety signals were detected for bempedoic acid treatment compared with placebo.

Date and Version of the Report:
11 Dec 2018, Final

Source: Applicant

15.4. Trial 048

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or Less Than Low Dose Statins (1002-048) (EudraCT No. 2016-004084-39, ClinicalTrials.gov No. NCT03001076)
Indication: (b) (4)
Investigational Product: Bempedoic acid
Name of Sponsor: Esperion Therapeutics, Inc.
Publications: none
Investigators and Study Sites: This study was conducted at 90 study sites in North America and Europe. Study sites and investigators are listed in Appendix 16.1.4.
Phase of Development: 3
Study Period: Date first subject enrolled: 29 Nov 2016 Date last subject completed: 11 Jan 2018
Background and Rationale for the Study: In this study, bempedoic acid was evaluated as an add-on therapy to ezetimibe for decreasing low-density lipoprotein cholesterol (LDL-C) in addition to background low-dose or less than low-dose statin therapy in patients with elevated LDL-C who required additional LDL-C lowering. Based on data from an integrated analysis of Phase 2 safety and efficacy, observed values and percent change from baseline in the primary efficacy endpoint, LDL-C, together with a positive safety profile, support the choice of the 180 mg dose for the Phase 3 studies. Bempedoic acid and ezetimibe lower LDL-C through different and potentially complementary mechanisms. Bempedoic acid inhibits adenosine triphosphate-citrate lyase in the liver, thereby decreasing cholesterol synthesis in the liver leading to increased LDL receptor expression and LDL particle clearance from the blood; whereas ezetimibe inhibits intestinal absorption of dietary cholesterol. Thus, use of bempedoic acid on a background of ezetimibe may be a very effective drug combination for lowering LDL-C in patients. The dose of 10 mg of ezetimibe is the only approved dose. The run-in period employed in the study was to provide a true LDL-C baseline for all patients.

Objectives:

Primary: To assess the 12-week efficacy of bempedoic acid 180 mg/day vs placebo in decreasing LDL-C when added to ezetimibe therapy in patients with elevated LDL-C.

Secondary:

- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day vs placebo when added to ezetimibe therapy on:
  - non-high-density lipoprotein cholesterol (HDL-C)
  - total cholesterol (TC)
  - apolipoprotein B (apo B)
  - high-sensitivity C-reactive protein (hsCRP);
- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day vs placebo on triglycerides (TGs) and HDL-C when added to ezetimibe;
- To evaluate 12-week safety and tolerability of bempedoic acid 180 mg/day compared with placebo when added to ezetimibe

Methodology: This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study. The study consisted of an approximate 1-week screening period, a 4-week single-blind placebo and ezetimibe run-in period, and a 12-week treatment period.

Screening Period

Patients started screening at Week -5 (Visit S1), approximately 5 weeks prior to randomization. Patients must have had LDL-C of ≥100 mg/dL (or ≥120 mg/dL if not on ezetimibe). The 1-week screening could have been extended for an additional 4 weeks if needed, to adjust background medical therapy. Eligible patients returned to the clinical site at Week -4 (Visit S2) to begin treatment with study-supplied ezetimibe and single-blind placebo. Patients who meet all enrollment criteria continued their background lipid-modifying therapy for lipid regulation and maintained consistent diet and exercise patterns throughout the study. LDL-C criteria at Week -5 were based on whether the patient was taking ezetimibe at screening or not.

Placebo and Ezetimibe Run-in Period

Eligible patients began the single-blind, placebo run-in period with study-supplied and labeled ezetimibe and placebo at Week -4 (Day -28 to ±3 days). If a patient was already taking ezetimibe, they stopped taking their personal supply of ezetimibe and began taking study-supplied ezetimibe. Patients were assessed to determine if they still met all enrollment criteria. At Week -1, patients returned for Visit S3 (Day -7 to ±3 days), for continued determination of enrollment criteria.

Treatment Period

Patients were randomized 2:1 on Day 1 (Visit T1) to receive double-blind investigational medicinal product (IMP), which was either bempedoic acid (N = 150) or placebo (N = 75) once-daily (QD) for 12 weeks. Patients continued taking study-supplied ezetimibe QD through the remainder of the treatment period in addition to the double-blind IMP. Randomized patients returned for clinic visits at Week 4, Week 8, and Week 12.

An independent expert Data Monitoring Committee reviewed unblinded safety data from this and other Phase 3 studies of bempedoic acid. A blinded independent expert Clinical Event Committee adjudicated designated clinical endpoints, including all major adverse cardiovascular events (MACE) and non-MACE endpoints defined as: cardiovascular (CV) death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE), using standardized definitions. Any clinical endpoints that met serious adverse event criteria were reported as serious adverse events.

Number of Subjects (Planned and Analyzed):

Planned: 225 patients

Analyzed: 269 patients enrolled and randomized, 268 patients treated

Diagnosis and Main Criteria for Inclusion: Adult men and women (age ≥18 years or legal age of majority based on regional law, whichever was greater) who signed the written informed consent document and were on low-dose or less than low-dose statin therapy (or who could not tolerate any statin therapy) and who required additional LDL-C lowering treatment. Patients must have had LDL-C of ≥100 mg/dL (or ≥120 mg/dL if not on ezetimibe). All patients had to have had fasting LDL-C ≥70 mg/dL (1.8 mmol/L) at Week -1 (Visit S3). Patients had to have reported attempting statin therapy and being unable to tolerate it due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued or the dose lowered. Patients could not have had any recent history of documented clinically significant cardiovascular disease, total fasting TG ≥500 mg/dL (5.6 mmol/L) at Week -5 (Visit S1), hemoglobin, type A_{1C} (HbA_{1C}) ≥10% at Week -5 (Visit S1), liver disease or dysfunction, renal dysfunction or glomerulonephritis, hematologic or coagulation disorders or a hemoglobin level <10.0 g/dL at Week -5 (Visit S1), or unexplained creatine kinase >3 × upper limit of normal at any time prior to randomization. The complete list of eligibility criteria is provided in Protocol Section 7.

Investigational Product, Non-investigational Product, Dose and Mode of Administration, Batch Number:

During the double-blind treatment period, bempedoic acid was supplied as 180 mg, film-coated tablets in 100-count bottles. The matching placebo was a tablet of identical physical appearance and packaging. Placebo was supplied in 35-count bottles for the single-blind placebo run-in period only. IMP was administered by mouth, QD.

Ezetimibe 10 mg was supplied as #3 gelatin capsules. In the United States and Canada, ezetimibe was manufactured and supplied as Zetia® and in the European Union, ezetimibe was supplied as Ezetrol®. Lot and batch numbers are provided in Appendix 16.1.6.

Duration of Treatment: Duration of treatment for an individual patient was up to approximately 17 weeks (1 week for screening, 4 weeks for single-blind placebo and ezetimibe run-in, and 12 weeks of treatment with double-blind IMP).

Study Endpoints:

Efficacy

The primary efficacy endpoint was the percent change from baseline to Week 12 in LDL-C. Baseline LDL-C was defined as the mean of the LDL-C values from Week -1 and predose Day 1/Week 0 (last two non-missing values on or prior to Day 1).

The key secondary efficacy endpoints, included in the hierarchical analysis, were: percent change from baseline to Week 12 in non-HDL-C; percent change from baseline to Week 12 in TC; percent change from baseline to Week 12 in apo B; and percent change from baseline to Week 12 in hsCRP. Other secondary efficacy endpoints were percent change from baseline to Week 12 in TG and HDL-C.

Safety

Safety endpoints were:

- subject incidence of treatment-emergent adverse events (including adverse events of special interest [AESI]
- clinical safety laboratory (including hematology, blood chemistry, and urinalysis) results
- vital signs and physical examination findings.

Statistical Methods:

Subject populations were defined for analysis as follows:

- Full Analysis Set (FAS): was used for all of the efficacy analyses and was defined as all randomized patients.
- Completer Analysis Set: used as a sensitivity analysis for the primary and secondary efficacy analyses, was defined as all patients in the FAS who completed both IMP and ezetimibe treatment and had non-missing Week 12 LDL-C values.
- Safety Analysis Set: used for all of the safety summaries, was defined as all randomized patients who received at least 1 dose of study medication.
- Pharmacokinetic (PK) Analysis Set: included all patients in the Safety Analysis Set who had at least one PK assessment.

Primary Efficacy Analysis

The primary efficacy endpoint was analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and baseline LDL-C as a covariate. The ANCOVA was performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Descriptive statistics were summarized for LDL-C at each visit and for change from baseline.

Secondary Efficacy Analyses

Key secondary endpoints were analyzed using the ANCOVA model described previously. Since significant departures from normality due to extreme outliers were observed, non-parametric (Wilcoxon rank-sum test) analysis was performed for hsCRP. Other secondary efficacy endpoints were analyzed using the ANCOVA model. An additional non-parametric (Wilcoxon rank-sum test) analysis was performed for TGs. Observed data from the FAS was used for other secondary efficacy endpoints. Descriptive statistics for all efficacy endpoints and change from baseline was presented at each visit

Pharmacokinetic Analyses

Descriptive statistics for plasma concentrations of bempedoic acid (ETC-1002) and its metabolite (ESP15228) were summarized for each visit, Weeks, 4, 8, and 12.

Safety Analyses

All outputs for safety outcomes were based on the Safety Analysis Set. No statistical comparisons were made between the treatment groups for safety data, unless otherwise specified within the relevant section.

Results:

Subject Disposition

Screened: 616 subjects

Randomized: 181 bempedoic acid, 88 placebo

Discontinued IMP: 17 (9.4%) bempedoic acid, 8 (9.1%) placebo

Withdrew from study: 5 (2.8%) bempedoic acid, 7 (8.0%) placebo

Demographic and Baseline Characteristics

Sex: 104 (38.7%) men, 165 (61.3%) women

Mean (standard deviation [SD]) age: 63.8 (10.93) years

Race: 240 (89.2%) white, 21 (7.8%) black or African American, 4 (1.5%) Asian, 2 (0.7%) Native Hawaiian or other Pacific Islander, and 2 (0.7%) multiple

Ethnicity: 66 (24.5%) Hispanic or Latino; 203 (75.5%) not Hispanic or Latino

Mean LDL-C (standard deviation): 127.56 (29.838) mg/dL

Efficacy Results:

In the primary efficacy analysis, treatment with bempedoic acid resulted in significantly greater reductions from baseline for LS means in LDL-C (-23.46%) compared with placebo (4.99%). The difference from placebo for LS means (-28.45%) was statistically significant (p <0.001). The LS mean difference from placebo in absolute reduction from baseline (based on observed data) was -36.37 mg/dL at Week 12.

In the key secondary efficacy analyses, the LS mean difference between bempedoic acid and placebo in percent change from baseline was statistically significant for non-HDL-C (-23.56%), TC (-17.99%), and apo B (-19.32%). For hsCRP, the median percent change from baseline was 2.09 for placebo and -32.52 for bempedoic acid, with a location shift of -31.045.

Primary and secondary efficacy analyses in the FAS population based on the percent change from baseline at Week 12 are summarized below:

Parameter Percent Change From Baseline at Week 12	Placebo (N = 88)	Bempedoic Acid (N = 181)	p-value
LDL-C, n	88	181	
Least squares mean (SE)	4.99 (2.299)	-23.46 (1.945)	<0.001
Non-HDL-C, n	88	181	
Least squares mean (SE)	5.19 (2.202)	-18.38 (1.668)	<0.001
TC, n	88	181	
Least squares mean (SE)	2.88 (1.553)	-15.11 (1.282)	<0.001
apo B, n	86	180	
Least squares mean (SE)	4.74 (1.786)	-14.58 (1.497)	<0.001
hsCRP*, n	81	175	
Median (IQR)	2.088 (81.367)	-32.521 (66.270)	<0.001
TG, n	88	181	
Least squares mean (SE)	9.23 (4.218)	4.70 (3.068)	0.388
HDL-C, n	88	181	
Least squares mean (SE)	-1.38 (1.389)	-7.27 (1.214)	0.002

ANCOVA = analysis of covariance; Apo-B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; SE = standard error; TC = total cholesterol; TG = triglycerides.
Note: Baseline is defined as the mean of parameter values from the last two non-missing values on or prior to Day 1. LS Means, 95% CIs and P-values are based on an ANCOVA with change from baseline as the dependent variable, treatment as a fixed effect and baseline as a covariate. In the ANCOVA model, the missing parameter at Week 12 is imputed using a multiple imputation method taking account adherence to treatment. Percent change from baseline statistics are based on the final combined estimators from Rubin's method. For hsCRP, the location shift and 95% CI are based on Hodges-Lehman estimation from Wilcoxon Rank Sum test. All patients received ezetimibe 10 mg/day as background therapy throughout the study.
*Due to highly skewed distribution of hsCRP, a non-parametric method was used as the primary method for percent change in hsCRP. The parametric method was also performed for completeness (Table 14.2.2.6a, Table 14.2.2.6b, Table 14.2.2.6c, and Table 14.2.2.6e)
Source: Table 14.2.2.1a, Table 14.2.2.3a, Table 14.2.2.4a, Table 14.2.2.5a, Table 14.2.2.6e, Table 14.2.2.7d, Table 14.2.2.7a, and Table 14.2.5.1.

Pharmacokinetic Results:

Mean concentrations for ETC-1002 were 12502.29, 13305.70, and 13244.27 ng/mL at the Week 4, Week 8, and Week 12 predose assessment. Mean concentrations for ESP15228 were 1902.87, 1922.11, and 2066.23 ng/mL at the Week 4, Week 8, and Week 12 predose assessment.

Safety Results:

- A similar percentage of patients experienced at least one treatment-emergent adverse event (48.6% bempedoic acid, 44.8% placebo).
- Serious adverse events were similar across groups (2.8% bempedoic acid, 3.4% placebo). There were no IMP- or ezetimibe-related serious adverse events in this study and no deaths.
- A total of 6.1% of bempedoic acid and 5.7% of placebo patients discontinued IMP due to adverse events; 1.7% and 3.4% of bempedoic acid and placebo patients, respectively, withdrew from study due to an adverse event.
- Most adverse events were mild (27.1% bempedoic acid, 27.6% placebo) to moderate (18.2% bempedoic acid, 11.5% placebo) in intensity. Six patients (3.3%) in the bempedoic acid group and 5 patients (5.7%) in the placebo group had severe adverse events.
- Patients in the bempedoic acid group had a slightly higher incidence of both IMP-related adverse events (21.5% bempedoic acid, 9.2% placebo) and ezetimibe-related adverse events (7.7% bempedoic acid, 1.1% placebo).
- At Week 12, treatment with bempedoic acid was associated with slight increases in mean change from baseline for alanine aminotransferase, aspartate aminotransferase, and uric acid and slight decreases in mean change from baseline for creatine kinase and glomerular filtration rate compared with placebo. There was an almost negligible difference between bempedoic acid and placebo in mean change from baseline to Week 12 for creatinine and hemoglobin.
- There were no treatment-related changes in vital signs and no clinically significant abnormal shifts in electrocardiogram measurements from baseline to end of study.

CONCLUSIONS:

Results from this 12-week, Phase 3, randomized, double-blind, placebo-controlled study of bempedoic acid 180 mg or placebo as add-on to ezetimibe therapy in patients with elevated LDL-C demonstrate:

- Once daily treatment with bempedoic acid 180 mg resulted in statistically significant reductions in LDL-C at Week 12 compared with placebo (LS means difference from placebo of -28.45%, $p < 0.001$). Absolute mean change from baseline to Week 12 was -36.37 mg/dL.
- The statistical significance of the overall treatment benefit of bempedoic acid at Week 12 was also observed across all key secondary endpoints: non-HDL-C, TC, apo B, and hsCRP ($p < 0.001$ for each). The difference from placebo in LS means was -23.56%, -17.99%, and -19.32% for non-HDL-C, TC, and apo B, respectively. The location shift for hsCRP was -31.045%.
- Bempedoic acid treatment was well-tolerated with a favorable safety profile. No deaths occurred during the study and no serious adverse events were deemed related to double-blind IMP. The incidence of adverse events and IMP discontinuations due to adverse events was similar between the placebo and bempedoic acid treatment groups. No new safety signals were detected for bempedoic acid treatment compared with placebo.

Date and Version of the Report: 18 January 2019, Final

Source: Applicant

16. Efficacy: Additional Information and Assessment

16.1. Primary Endpoint

All primary outcomes are based on ANCOVA model with washout imputations for missing data.

Table 98. Percent Change in LDL-C Primary Results, Week 12

Study	Bempedoic Acid	Placebo
40	-16.3 (-17.4, -15.2)	1.6 (0.1, 3.1)
Difference	-17.9 (-19.7, -16.1)	
46	-22.5 (-24.8, -20.2)	-1.5 (-4.8, 1.8)
Difference	-21.0 (-25.0, -17.0)	
47	-14.8 (-16.9, -12.7)	2.2 (-0.7, 5.1)
Difference	-17.0 (-20.6, -13.4)	
48	-23.5 (-27.1, -20.0)	5.1 (-0.0, 10.3)
Difference	-28.6 (-34.9, -22.4)	

Source: FDA analyses
Abbreviations: LDL-C, low-density lipoprotein cholesterol

Table 99. Percent Change in LDL-C, Week 52

Study	Bempedoic Acid	Placebo
40	-11.5 (-12.8, -10.2)	1.0 (-0.8, 2.8)
Difference	-12.5 (-14.7, -10.2)	
47	-11.9 (-14.7, -9.2)	-0.7 (-4.4, 3.1)
Difference	-11.3 (-15.9, -6.6)	

Source: FDA analyses
Abbreviations: LDL-C, low-density lipoprotein cholesterol

16.2. Secondary Endpoints

16.2.1. Week 12

Week 12, Trial 040

Table 100. Percent Change From Baseline for Secondary Endpoints, Trial 040, Week 12

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-18.7 (-20.5, -16.9)	-17.1 (-18.2, -16.1)	1.6 (0.1, 3.1)
HDL	-5.9 (-7.0, -4.7)	-5.9 (-6.6, -5.3)	-0.1 (-1.0, 0.9)
Triglycerides	2.5 (-0.1, 5.1)[1]	2.9 (42)[2]	-0.3 (37.6)[2]
Apo-B	-12.4 (-14.0, -10.8)	-9.0 (-10.0, -8.1)	3.4 (2.0, 4.7)
Total cholesterol	-11.5 (-12.8, -10.3)	-10.7 (-11.4, -10.0)	0.8 (-0.2, 1.9)
Non-HDL	-13.8 (-15.5, -12.1)	-12.3 (-13.3, -11.4)	1.5 (0.1, 2.8)
hsCRP	-21.5 (-26.9, -16)[1]	-22.1 (73.4)[2]	2.6 (91.4)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Table 101. Change From Baseline for Secondary Endpoints, Trial 040, Week 12

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-19.1 (-21.1, -17.0)	-19.0 (-20.2, -17.8)	0.0 (-1.6, 1.7)
HDL	-2.8 (-3.3, -2.2)	-3.0 (-3.3, -2.7)	-0.2 (-0.7, 0.2)
Triglycerides	4.5 (1.0, 8.5)[1]	3.0 (51.5)[2]	-0.5 (45)[2]
Apo-B	-10.8 (-12.2, -9.4)	-9.3 (-10.1, -8.5)	1.5 (0.4, 2.6)
Total cholesterol	-20.7 (-23.1, -18.3)	-20.5 (-22.0, -19.1)	0.2 (-1.8, 2.2)
Non-HDL	-17.8 (-20.1, -15.4)	-17.5 (-18.9, -16.1)	0.3 (-1.6, 2.2)
hsCRP	-0.38 (-0.49, -0.27)[1]	-0.22 (1.35)[2]	0.02 (1.29)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Week 12, Trial 046

Table 102. Percent Change From Baseline for Secondary Endpoints, Trial 046, Week 12

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LBL-C	-22.0 (-26.0, -17.9)	-23.5 (-25.8, -21.2)	-1.5 (-4.8, 1.8)
HDL	-4.6 (-8.0, -1.2)	-4.9 (-6.8, -2.9)	-0.3 (-3.1, 2.5)
Triglycerides	-0.1 (-7.0, 6.9)[1]	-0.3 (43.8)[2]	-3.3 (33.6)[2]
Apo-B	-15.3 (-18.7, -11.9)	-15.5 (-17.4, -13.5)	-0.1 (-2.9, 2.6)
Total cholesterol	-15.1 (-17.9, -12.4)	-16.0 (-17.5, -14.4)	-0.8 (-3.1, 1.4)
Non-HDL	-18.4 (-21.8, -14.9)	-18.9 (-20.9, -17.0)	-0.6 (-3.4, 2.3)
hsCRP	-24.3 (-35.9, -12.7)[1]	-25.4 (63.5)[2]	2.7 (69.1)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Table 103. Change From Baseline for Secondary Endpoints, Trial 046, Week 12

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-35.2 (-41.6, -28.7)	-38.9 (-42.6, -35.2)	-3.7 (-9.0, 1.6)
HDL	-2.0 (-3.8, -0.3)	-2.8 (-3.8, -1.8)	-0.8 (-2.2, 0.7)
Triglycerides	3.0 (-9.0, 15.5)[1]	-0.3 (71.5)[2]	-4.5 (53)[2]
Apo-B	-22.2 (-27.1, -17.4)	-23.3 (-26.1, -20.6)	-1.1 (-5.0, 2.9)
Total cholesterol	-37.5 (-44.3, -30.7)	-40.9 (-44.8, -37.1)	-3.5 (-9.1, 2.2)
Non-HDL	-35.7 (-42.4, -29.1)	-38.2 (-42.0, -34.5)	-2.5 (-8.0, 3.0)
hsCRP	-0.71 (-1.22, -0.31)[1]	-0.52 (2.2)[2]	0.08 (1.54)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Week 12, Trial 047

Table 104. Percent Change From Baseline for Secondary Endpoints, Trial 047, Week 12

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-17.9 (-21.5, -14.4)	-15.6 (-17.7, -13.5)	2.3 (-0.5, 5.2)
HDL	-6.1 (-8.5, -3.8)	-6.4 (-7.8, -5.0)	-0.2 (-2.2, 1.7)
Triglycerides	1.3 (-3.9, 6.3)[1]	0.9 (49)[2]	3.2 (37.9)[2]
Apo-B	-13.5 (-16.4, -10.5)	-9.7 (-11.5, -8.0)	3.7 (1.3, 6.1)
Total cholesterol	-11.5 (-13.9, -9.2)	-10.3 (-11.6, -8.9)	1.3 (-0.6, 3.2)
Non-HDL	-13.4 (-16.6, -10.2)	-11.1 (-13.0, -9.3)	2.3 (-0.3, 4.9)
hsCRP	-8.7 (-17.2, -0.4)[1]	-18.7 (69.9)[2]	-9.4 (71.6)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Table 105. Change From Baseline for Secondary Endpoints, Trial 047, Week 12

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-22.7 (-26.9, -18.5)	-21.7 (-24.2, -19.3)	1.0 (-2.4, 4.4)
HDL	-2.6 (-3.8, -1.4)	-3.3 (-3.9, -2.6)	-0.7 (-1.6, 0.3)
Triglycerides	2.0 (-6.0, 9.5)[1]	2.0 (65.5)[2]	3.0 (54)[2]
Apo-B	-15.6 (-19.0, -12.2)	-13.2 (-15.2, -11.2)	2.4 (-0.4, 5.2)
Total cholesterol	-23.7 (-28.5, -18.9)	-23.1 (-25.9, -20.3)	0.6 (-3.4, 4.5)
Non-HDL	-21.1 (-25.9, -16.3)	-19.9 (-22.7, -17.1)	1.2 (-2.7, 5.2)
hsCRP	-0.15 (-0.34, 0.03)[1]	-0.22 (1.39)[2]	-0.13 (1.27)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Week 12, Trial 048

Table 106. Percent Change From Baseline for Secondary Endpoints, Trial 048, Week 12

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-29.4 (-35.7, -23.0)	-24.4 (-28.0, -20.8)	5.0 (-0.2, 10.2)
HDL	-5.9 (-9.8, -1.9)	-7.3 (-9.5, -5.0)	-1.4 (-4.7, 1.9)
Triglycerides	-6.4 (-14.3, 1.4)[1]	-1.4 (37.6)[2]	7.8 (33.4)[2]
Apo-B	-19.9 (-24.8, -14.9)	-15.1 (-17.9, -12.3)	4.8 (0.7, 8.9)
Total cholesterol	-18.4 (-22.6, -14.2)	-15.6 (-18.0, -13.2)	2.8 (-0.7, 6.3)
Non-HDL	-24.2 (-29.8, -18.6)	-19.1 (-22.3, -16.0)	5.1 (0.5, 9.7)
hsCRP	-31.0 (-44.8, -17.4)[1]	-32.5 (66.3)[2]	2.1 (81.4)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Table 107. Change From Baseline for Secondary Endpoints, Trial 048, Week 12

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-36.2 (-44.1, -28.4)	-32.3 (-36.7, -27.9)	3.9 (-2.5, 10.4)
HDL	-3.1 (-5.3, -0.8)	-4.1 (-5.4, -2.8)	-1.0 (-2.9, 0.8)
Triglycerides	-2.3 (-22.0, 17.4)[1]	6.6 (-4.5, 17.6)[2]	8.9 (-7.4, 25.1)[2]
Apo-B	-23.4 (-29.2, -17.6)	-19.5 (-22.8, -16.2)	3.9 (-0.9, 8.7)
Total cholesterol	-39.1 (-48.0, -30.1)	-35.5 (-40.5, -30.4)	3.6 (-3.8, 11.0)
Non-HDL	-36.6 (-45.3, -27.8)	-31.7 (-36.6, -26.7)	4.9 (-2.3, 12.1)
hsCRP	-0.6 (-1.02, -0.23)[1]	-0.51 (1.81)[2]	0.03 (1.48)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

16.2.2. Week 24

Week 24, Trial 040

Table 108. Percent Change From Baseline for Secondary Endpoints, Trial 040, Week 24

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-16.9 (-18.9, -14.9)	-15.7 (-16.8, -14.5)	1.2 (-0.4, 2.8)
HDL	-5.4 (-6.7, -4.2)	-4.5 (-5.2, -3.7)	1.0 (-0.1, 2.0)
Triglycerides	0.8 (-1.9, 3.5)[1]	2.2 (42.5)[2]	0.8 (35.3)[2]
Apo-B	-11.4 (-13.2, -9.7)	-7.0 (-8.0, -6.0)	4.4 (3.0, 5.9)
Total cholesterol	-10.9 (-12.3, -9.5)	-9.8 (-10.6, -9.0)	1.1 (-0.0, 2.2)
Non-HDL	-13.1 (-14.9, -11.3)	-11.6 (-12.7, -10.6)	1.5 (0.0, 2.9)
hsCRP	-19.5 (-25.4, -13.7)[1]	-16.4 (85.8)[2]	2.7 (92.0)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Table 109. Change From Baseline for Secondary Endpoints, Trial 040, Week 24

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-17.5 (-19.6, -15.3)	-17.4 (-18.6, -16.1)	0.1 (-1.7, 1.9)
HDL	-2.5 (-3.1, -1.9)	-2.3 (-2.7, -2.0)	0.2 (-0.3, 0.7)
Triglycerides	2.0 (-1.5, 5.5)[1]	2.5 (52.8)[2]	1.0 (43.5)[2]
Apo-B	-10.1 (-11.6, -8.6)	-7.5 (-8.4, -6.6)	2.6 (1.3, 3.8)
Total cholesterol	-19.9 (-22.5, -17.3)	-18.9 (-20.4, -17.4)	1.0 (-1.1, 3.1)
Non-HDL	-17.3 (-19.8, -14.8)	-16.5 (-18.0, -15.1)	0.8 (-1.2, 2.8)
hsCRP	-0.36 (-0.48, -0.24)[1]	-0.17 (1.41)[2]	0.035 (1.29)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Week 24, Trial 046

Table 110. Percent Change From Baseline for Secondary Endpoints, Trial 046, Week 24

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-20.0 (-24.4, -15.7)	-22.2 (-24.6, -19.7)	-2.1 (-5.7, 1.4)
HDL	-5.6 (-9.5, -1.8)	-4.7 (-6.9, -2.6)	0.9 (-2.2, 4.0)
Triglycerides	-3.7 (-11.1, 3.9)[1]	-4.6 (45.7)[2]	2.1 (37)[2]
Apo-B	-15.5 (-19.1, -12.0)	-15.0 (-17.0, -13.0)	0.5 (-2.4, 3.5)
Total cholesterol	-14.5 (-17.5, -11.5)	-15.2 (-16.9, -13.5)	-0.7 (-3.1, 1.8)
Non-HDL	-17.1 (-20.8, -13.4)	-17.8 (-19.9, -15.7)	-0.7 (-3.8, 2.4)
hsCRP	-27.1 (-40.5, -13.7)[1]	-25.1 (73.6)[2]	4.3 (67.8)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Table 111. Change From Baseline for Secondary Endpoints, Trial 046, Week 24

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-30.7 (-37.6, -23.9)	-36.7 (-40.6, -32.8)	-6.0 (-11.6, -0.4)
HDL	-3.2 (-5.2, -1.2)	-3.1 (-4.2, -1.9)	0.1 (-1.5, 1.7)
Triglycerides	-4.5 (-17.0, 8.0)[1]	-6.5 (67.5)[2]	4.3 (61)[2]
Apo-B	-21.7 (-26.7, -16.8)	-22.6 (-25.4, -19.8)	-0.9 (-4.9, 3.2)
Total cholesterol	-35.5 (-43.0, -28.0)	-39.2 (-43.5, -34.9)	-3.7 (-9.8, 2.5)
Non-HDL	-32.7 (-39.9, -25.5)	-36.2 (-40.3, -32.1)	-3.5 (-9.4, 2.4)
hsCRP	-0.71 (-1.18, -0.31)[1]	-0.45 (2.28)[2]	0.08 (1.5)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Week 24, Trial 047

Table 112. Percent Change From Baseline for Secondary Endpoints, Trial 047, Week 24

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-15.7 (-20.6, -10.9)	-12.9 (-15.8, -10.1)	2.8 (-1.2, 6.8)
HDL	-5.2 (-7.8, -2.7)	-4.8 (-6.2, -3.3)	0.5 (-1.6, 2.6)
Triglycerides	-1.9 (-7.0, 3.1)[1]	-2.6 (46.1)[2]	0.0 (39.8)[2]
Apo-B	-13.1 (-17.7, -8.5)	-8.4 (-11.0, -5.7)	4.7 (0.9, 8.4)
Total cholesterol	-10.8 (-13.7, -7.9)	-9.2 (-10.9, -7.6)	1.5 (-0.8, 3.9)
Non-HDL	-12.6 (-16.6, -8.6)	-10.2 (-12.5, -7.9)	2.4 (-0.8, 5.7)
hsCRP	-21.3 (-32.2, -10.0)[1]	-24.1 (65.5)[2]	1.6 (79.7)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Table 113. Change From Baseline for Secondary Endpoints, Trial 047, Week 24

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-19.4 (-24.4, -14.5)	-19.2 (-22.1, -16.3)	0.2 (-3.8, 4.2)
HDL	-2.2 (-3.5, -1.0)	-2.4 (-3.2, -1.7)	-0.2 (-1.2, 0.8)
Triglycerides	-1.0 (-8.5, 6.5)[1]	-2.8 (62.5)[2]	0.0 (52.5)[2]
Apo-B	-14.3 (-19.3, -9.3)	-12.0 (-14.9, -9.1)	2.3 (-1.8, 6.4)
Total cholesterol	-21.5 (-27.1, -15.8)	-21.4 (-24.7, -18.2)	0.1 (-4.5, 4.7)
Non-HDL	-19.3 (-24.8, -13.7)	-19.0 (-22.2, -15.7)	0.3 (-4.2, 4.8)
hsCRP	-0.43 (-0.71, -0.19)[1]	-0.32 (1.43)[2]	0.01 (1.15)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

16.2.3. Week 52

Week 52, Trial 040

Table 114. Percent Change From Baseline for Secondary Endpoints, Trial 040, Week 52

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-13.6 (-15.8, -11.3)	-12.6 (-13.9, -11.3)	1.0 (-0.9, 2.8)
HDL	-5.7 (-6.9, -4.4)	-5.3 (-6.0, -4.6)	0.4 (-0.7, 1.4)
Triglycerides	-0.8 (-3.5, 1.8)[1]	-4.5 (40.6)[2]	-3.2 (34.4)[2]
Apo-B	-9.0 (-10.9, -7.0)	-5.9 (-7.0, -4.8)	3.1 (1.5, 4.7)
Total cholesterol	-9.2 (-10.7, -7.7)	-8.9 (-9.7, -8.0)	0.3 (-0.9, 1.5)
Non-HDL	-10.5 (-12.5, -8.5)	-10.0 (-11.1, -8.9)	0.5 (-1.1, 2.1)
hsCRP	-14.8 (-21.2, -8.5)[1]	-14.4 (93.9)[2]	1.8 (97.5)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Table 115. Change From Baseline for Secondary Endpoints, Trial 040, Week 52

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-13.9 (-16.3, -11.5)	-14.4 (-15.7, -13.0)	-0.4 (-2.4, 1.5)
HDL	-2.6 (-3.2, -2.0)	-2.7 (-3.0, -2.3)	-0.1 (-0.6, 0.4)
Triglycerides	-0.5 (-4.0, 3.0)[1]	-5.0 (50.5)[2]	-3.0 (43.5)[2]
Apo-B	-8.1 (-9.7, -6.4)	-6.6 (-7.6, -5.7)	1.4 (0.1, 2.8)
Total cholesterol	-16.7 (-19.4, -13.9)	-17.3 (-18.9, -15.7)	-0.7 (-2.9, 1.6)
Non-HDL	-14.0 (-16.6, -11.3)	-14.6 (-16.2, -13.1)	-0.6 (-2.8, 1.6)
hsCRP	-0.25 (-0.37, -0.14)[1]	-0.13 (1.48)[2]	0.02 (1.3)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

Week 52, Trial 047

Table 116. Percent Change From Baseline for Secondary Endpoints, Trial 047, Week 52

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-12.3 (-16.9, -7.6)	-13.2 (-15.9, -10.5)	-0.9 (-4.7, 2.9)
HDL	-4.0 (-6.5, -1.5)	-7.4 (-8.9, -5.9)	-3.4 (-5.5, -1.4)
Triglycerides	0.3 (-5.0, 5.5)[1]	-0.9 (44.9)[2]	-3.6 (43.2)[2]
Apo-B	-9.6 (-13.0, -6.2)	-6.6 (-8.5, -4.6)	3.0 (0.2, 5.8)
Total cholesterol	-8.4 (-11.2, -5.5)	-10.2 (-11.9, -8.6)	-1.9 (-4.2, 0.4)
Non-HDL	-9.9 (-13.8, -6.0)	-10.3 (-12.6, -8.0)	-0.4 (-3.5, 2.8)
hsCRP	-7.6 (-17.0, 1.7)[1]	-16.7 (82.3)[2]	-6.3 (81.1)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

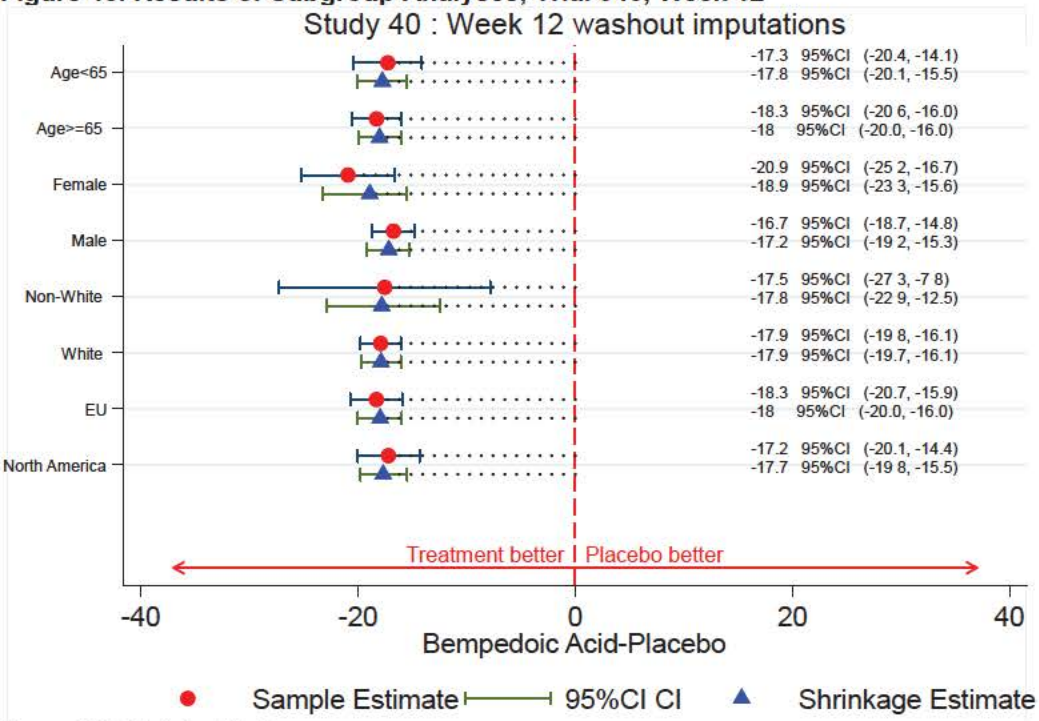
Table 117. Change From Baseline for Secondary Endpoints, Trial 047, Week 52

Endpoint	Difference Mean (95% CI)	Bempedoic Mean (95% CI)	Placebo Mean (95% CI)
LDL-C	-15.1 (-20.1, -10.0)	-19.7 (-22.6, -16.8)	-4.6 (-8.7, -0.5)
HDL	-1.8 (-3.1, -0.6)	-4.1 (-4.8, -3.4)	-2.2 (-3.2, -1.2)
Triglycerides	1.0 (-7.0, 9.0)[1]	-1.5 (61)[2]	-4.0 (54.5)[2]
Apo-B	-10.8 (-14.6, -6.9)	-10.1 (-12.3, -7.9)	0.7 (-2.4, 3.8)
Total cholesterol	-16.6 (-22.3, -10.8)	-23.2 (-26.6, -19.9)	-6.7 (-11.3, -2.0)
Non-HDL	-14.7 (-20.3, -9.0)	-19.1 (-22.4, -15.9)	-4.5 (-9.1, 0.1)
hsCRP	-0.16 (-0.36, 0.03)[1]	-0.2 (1.45)[2]	-0.07 (1.32)[2]

Source: FDA analyses
[1] Location shift (asymptotic 95% CI)
[2] Median change (IQR)
Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

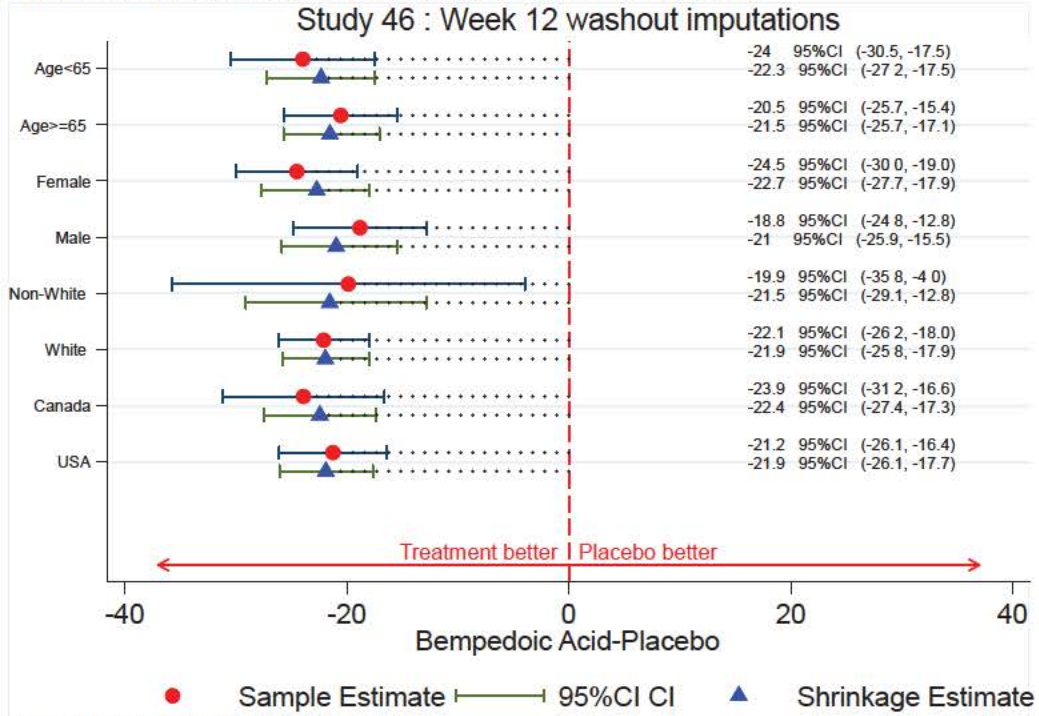
16.3. Subgroup Analyses

Figure 45. Results of Subgroup Analyses, Trial 040, Week 12



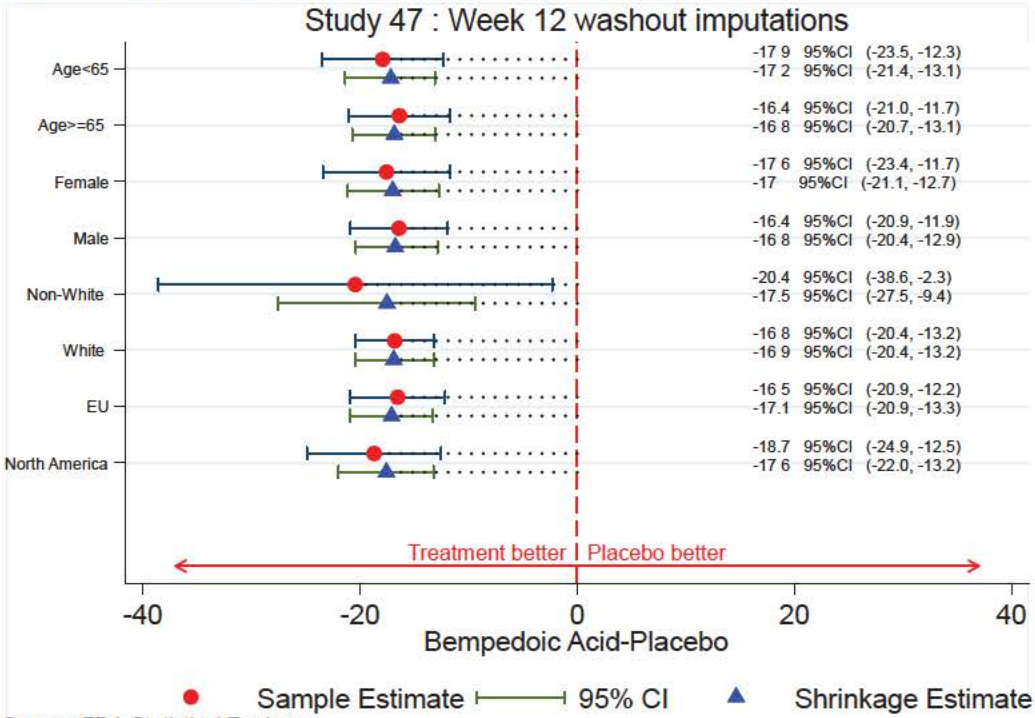
Source: FDA Statistical Reviewer
Abbreviations: CI, confidence interval; EU, European Union

Figure 46. Results of Subgroup Analyses, Trial 046, Week 12



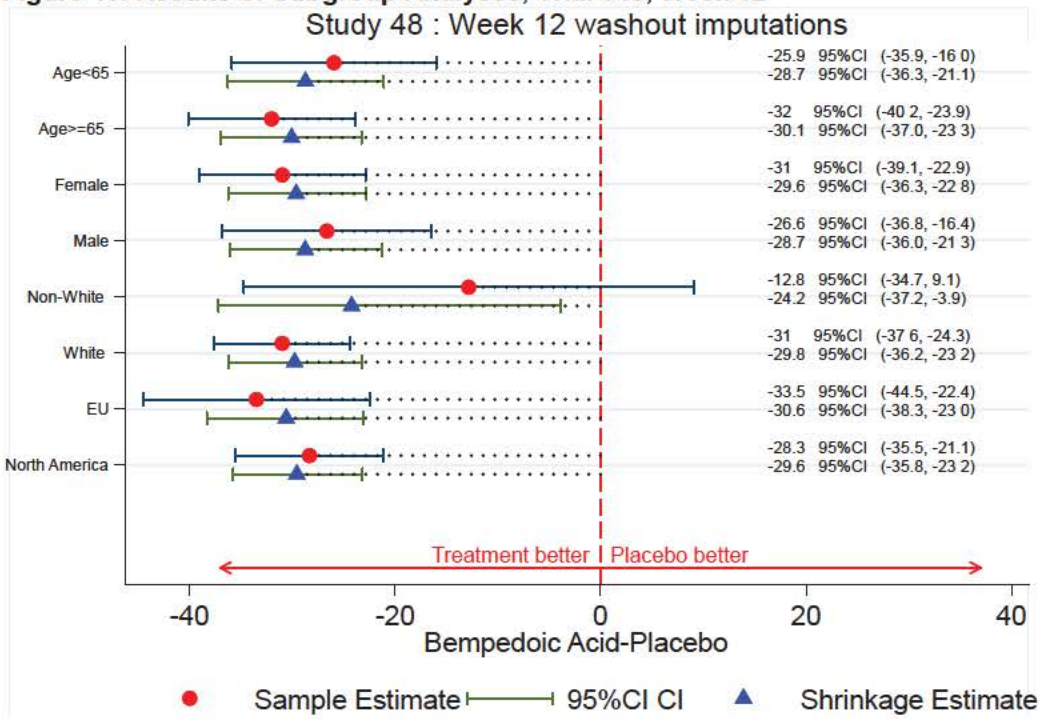
Source: FDA Statistical Reviewer
Abbreviations: CI, confidence interval; EU, European Union

Figure 47. Results of Subgroup Analyses, Trial 047, Week 12



Source: FDA Statistical Reviewer
Abbreviations: CI, confidence interval; EU, European Union

Figure 48. Results of Subgroup Analyses, Trial 048, Week 12



Source: FDA Statistical Reviewer
Abbreviations: CI, confidence interval; EU, European Union

Table 118. Change in LDL-C, Results Based on Levels of CV Risk and Statin Use

Subgroup	Treatment Arm	Trial 040	Trial 047
ASCVD + high-intensity statins			
12	Bempedoic	-15.8 (-17.3, -14.3)	-12.9 (-16.0, -9.8)
	Placebo	1.3 (-0.9, 3.4)	3.3 (-1.1, 7.8)
	Difference	-17.1 (-19.7, -14.4)	-16.2 (-21.6, -10.8)
52	Bempedoic	-10.3 (-12.2, -8.3)	-8.2 (-12.4, -4.0)
	Placebo	2.3 (-0.5, 5.0)	2.7 (-3.3, 8.7)
	Difference	-12.6 (-16.0, -9.2)	-10.9 (-18.3, -3.6)
ASCVD + medium- or low-intensity statins			
12	Bempedoic	-16.9 (-18.4, -15.3)	-16.5 (-19.4, -13.6)
	Placebo	2.2 (0.1, 4.3)	1.4 (-2.6, 5.4)
	Difference	-19.1 (-21.7, -16.4)	-17.9 (-22.8, -12.9)
52	Bempedoic	-12.4 (-14.3, -10.6)	-16.0 (-19.6, -12.5)
	Placebo	-0.4 (-3.0, 2.1)	-3.6 (-8.3, 1.1)
	Difference	-12.0 (-15.1, -8.9)	-12.5 (-18.3, -6.6)
HeFH + high-intensity statins			
12	Bempedoic	-10.7 (-16.4, -5.0)	-20.7 (-36.0, -5.4)
	Placebo	-6.7 (-15.1, 1.6)	-2.8 (-21.2, 15.6)
	Difference	-3.9 (-14.1, 6.2)	-17.9 (-41.8, 6.0)
52	Bempedoic	-11.8 (-19.5, -4.1)	-21.8 (-38.3, -5.4)
	Placebo	4.5 (-5.8, 14.9)	-9.5 (-29.6, 10.5)
	Difference	-16.3 (-29.4, -3.3)	-12.3 (-38.0, 13.4)
HeFH + medium or low-intensity statins			
12	Bempedoic	-24.1 (-35.0, -13.1)	0.8 (-12.9, 14.4)
	Placebo	8.5 (-5.9, 22.8)	-18.9 (-37.1, -0.6)
	Difference	-32.5 (-50.8, -14.3)	-20.7 (-36.0, -5.4)
52	Bempedoic	-16.5 (-26.1, -6.9)	-3.4 (-18.6, 11.7)
	Placebo	0.7 (-11.9, 13.2)	-3.5 (-25.5, 18.6)
	Difference	-17.2 (-33.2, -1.2)	-21.8 (-38.3, -5.4)

Source: FDA analyses
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol

Table 119. Change in LDL-C, Stratified Subgroup Analysis, Trial 046

Stratification	Treatment Arm	Week 12	Week 24
Primary prevention (LDL-C >=130 mg/dL)	Bempedoic acid	-25.1 (-27.7, -22.52)	-20.8 (-23.7, -17.8)
	Placebo	-2.3 (-6.2, 1.5)	-2.3 (-6.6, 2)
	Difference	-22.8 (-27.5, -18.2)	-18.4 (-23.7, -13.2)
Secondary prevention and/or HeFH (LDL-C >=100 mg/dL)	Bempedoic acid	-18.4 (-22.6, -14.1)	-20.2 (-24,6, -15.8)
	Placebo	-0.2 (-6.2, 5.9)	-2.2 (-8.3, 4)
	Difference	-18.2 (-25.6, -10.8)	-18 (-25.6, -10.4)

Source: FDA analyses
Abbreviations: HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol

17. Clinical Safety: Additional Information and Assessment

17.1. Supplemental Data for High CV Risk Trials (1002-040 and 1002-047) and No/Low Statin Trials (1002-046 and 1002-048)

17.1.1. Duration of Exposure

Table 120. Duration of Exposure, Safety Population, Trials 1002-040 and 1002-047

	Trial 1002-040		Trial 1002-047		Pooled Safety Population	
	Bempedoic Acid (N=1487)	Placebo (N=742)	Bempedoic Acid (N=522)	Placebo (N=257)	Bempedoic Acid (N=2009)	Placebo (N=999)
Duration of treatment (weeks)						
Mean (SD)	43.6 (16.5)	45.5 (14.6)	45.1 (14.7)	47.3 (11.8)	44.0 (16.0)	45.9 (13.9)
Median (min, max)	51.9 (0.0, 76.7)	51.9 (0.0, 57.0)	51.7 (0.0, 64.7)	51.9 (1.7, 57.4)	51.9 (0.0, 76.7)	51.9 (0.0, 57.4)
Patients treated, by duration, n (%)						
<12 weeks	154 (10.4)	54 (7.3)	40 (7.7)	12 (4.7)	194 (9.7)	66 (6.6)
≥12 weeks	114 (7.7)	46 (6.2)	28 (5.4)	7 (2.7)	142 (7.1)	53 (5.3)
≥24 weeks	78 (5.2)	42 (5.7)	38 (7.3)	21 (8.2)	116 (5.8)	63 (6.3)
≥48 weeks	1139 (76.6)	600 (80.9)	416 (79.7)	217 (84.4)	1555 (77.4)	817 (81.8)
≥72 weeks	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)

Source: adex.xpt; Software: Python
Abbreviations: N, number of subjects in treatment group; n, number of patients treated; SD, standard deviation

Table 121. Duration of Exposure, Safety Population, Trial 046

Parameter	Bempedoic Acid (N=234)	Placebo (N=111)
Duration of treatment (weeks)		
Mean (SD)	20.9 (6.4)	21.9 (5.5)
Median (min, max)	23.9 (0.3, 26.9)	23.9 (1.0, 26.9)
Patients treated, by duration, n (%)		
<6 weeks	17 (7.3)	6 (5.4)
≥6 weeks	12 (5.1)	3 (2.7)
≥12 weeks	16 (6.8)	5 (4.5)
≥18 weeks	101 (43.2)	54 (48.6)
>24 weeks	88 (37.6)	43 (38.7)

Source: adsl.xpt; Software: Python
Abbreviations: N, number of subjects in treatment group; n, number of patients treated; SD, standard deviation

Table 122. Duration of Exposure, Safety Population, Trial 048

Parameter	Bempedoic Acid (N=181)	Placebo (N=87)
Duration of treatment (weeks)		
Mean (SD)	11.2 (2.4)	11.6 (1.4)
Median (min, max)	11.9 (0.1, 13.9)	11.9 (4.1, 13.4)
Patients treated, by duration, n (%)		
<6 weeks	11 (6.1)	2 (2.3)
≥6 weeks	118 (65.2)	53 (60.9)
≥12 weeks	52 (28.7)	32 (36.8)
≥18 weeks	0 (0.0)	0 (0.0)
>24 weeks	0 (0.0)	0 (0.0)

Source: adsl.xpt; Software: Python
Abbreviations: N, number of subjects in treatment group; n, number of patients treated; SD, standard deviation

17.1.2. Vital Signs

Table 123. Vital Signs, Change From Baseline Over Time, Safety Population, Trial 040

Vital Signs	Bempedoic Acid (N=1487)	Placebo (N=742)
Body mass index (kg/m2)		
Week 4	-0.03	-0.03
Week 8	-0.03	-0.04
Week 12	-0.09	0.02
Week 24	-0.13	0.00
Week 36	-0.18	-0.06
Week 52	-0.27	-0.09
Diastolic blood pressure (mmHg)		
Week 4	-0.17	-0.06
Week 8	-0.56	0.11
Week 12	-0.31	-0.05
Week 24	-0.57	-0.16
Week 36	-0.41	-0.20
Week 52	-0.21	0.25

Vital Signs	Bempedoic Acid (N=1487)	Placebo (N=742)
Heart rate (beats/min)		
Week 4	0.56	0.91
Week 8	0.58	1.00
Week 12	0.17	0.43
Week 24	0.33	0.91
Week 36	-0.04	0.82
Week 52	0.13	0.71
Systolic blood pressure (mmHg)		
Week 4	-0.62	0.30
Week 8	-0.73	0.17
Week 12	-0.77	-0.15
Week 24	-0.97	-0.81
Week 36	-1.26	-0.80
Week 52	-0.35	0.80
Weight (kg)		
Week 4	-0.10	-0.04
Week 8	-0.10	-0.09
Week 12	-0.27	0.09
Week 24	-0.38	0.02
Week 36	-0.54	-0.15
Week 52	-0.78	-0.22

Source: advs.xpt; Software: Python
Abbreviations: N, number of subjects in group

Table 124. Vital Signs Change From Baseline Over Time, Safety Population, Trial 046

Vital Signs	Bempedoic Acid (N=234)	Placebo (N=111)
Diastolic blood pressure (mmHg)		
Week 4	-0.69	-0.31
Week 8	1.06	2.75
Week 12	-0.01	-0.04
Week 24/end of study	-0.39	0.33
Heart rate (beats/min)		
Week 4	-0.11	1.28
Week 8	-2.00	-4.50
Week 12	-0.24	2.44
Week 24/end of study	-0.41	1.51
Systolic blood pressure (mmHg)		
Week 4	0.16	-0.08
Week 8	-3.12	17.75
Week 12	1.07	-0.96
Week 24/end of study	1.48	1.44

Source: advs.xpt; Software: Python
Abbreviations: N, number of subjects in group

Table 125. Vital Signs, Change From Baseline Over Time, Safety Population, Trial 047

Vital Signs	Bempedoic Acid (N=522)	Placebo (N=257)
Body mass index (kg/m2)		
Week 4 (Visit T2)	-0.08	0.00
Week 8 (Visit T3)	-0.36	-0.30
Week 12 (Visit T4)	-0.05	0.04
Week 24 (Visit T5)	-0.07	0.07
Week 36 (Visit T6)	-0.27	-0.37
Week 52 (Visit T7)	-0.18	0.03
Diastolic blood pressure (mmHg)		
Week 4 (Visit T2)	-0.18	0.08
Week 8 (Visit T3)	1.25	1.50
Week 12 (Visit T4)	0.74	0.89
Week 24 (Visit T5)	0.63	1.09
Week 36 (Visit T6)	0.97	2.23
Week 52 (Visit T7)	0.37	-0.40
Heart rate (beats/min)		
Week 4 (Visit T2)	0.49	0.84
Week 8 (Visit T3)	3.67	5.50
Week 12 (Visit T4)	0.57	1.60
Week 24 (Visit T5)	1.98	2.01
Week 36 (Visit T6)	-0.03	0.38
Week 52 (Visit T7)	0.47	-0.41
Systolic blood pressure (mmHg)		
Week 4 (Visit T2)	-0.17	1.07
Week 8 (Visit T3)	3.42	6.75
Week 12 (Visit T4)	2.31	2.02
Week 24 (Visit T5)	3.48	2.29
Week 36 (Visit T6)	2.84	5.77
Week 52 (Visit T7)	2.19	0.01
Weight (kg)		
Week 4 (Visit T2)	-0.21	0.02
Week 8 (Visit T3)	-0.84	-0.90
Week 12 (Visit T4)	-0.13	0.13
Week 24 (Visit T5)	-0.18	0.25
Week 36 (Visit T6)	-0.63	-1.02
Week 52 (Visit T7)	-0.51	0.13

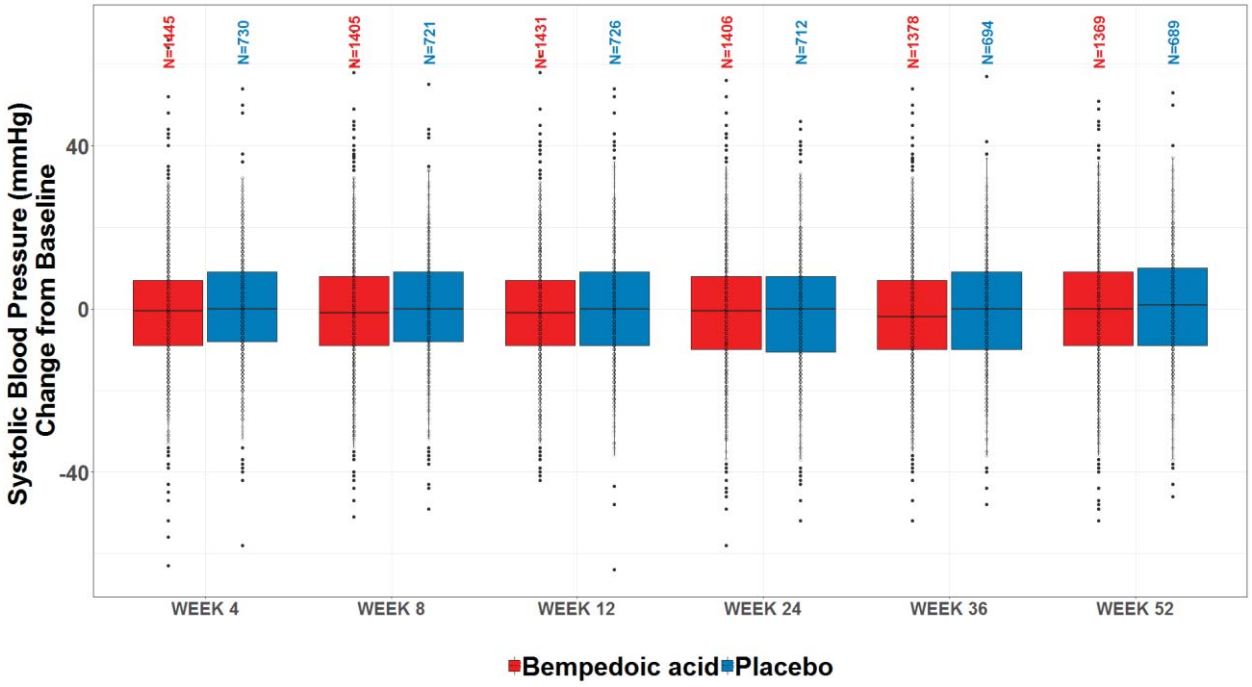
Source: advs.xpt; Software: Python
Abbreviations: N, number of subjects in group; T, treatment visit

Table 126. Vital Signs Change From Baseline Over Time, Safety Population, Trial 048

Vital Signs	Bempedoic Acid (N=181)	Placebo (N=87)
Body mass index (kg/m2)		
Week 4	-0.11	0.23
Week 8	-0.21	-0.17
Week 12/end of study	-0.07	0.10
Diastolic blood pressure (mmHg)		
Week 4	-0.39	0.60
Week 8	0.98	1.42
Week 12/end of study	0.60	0.98
Heart rate (beats/min)		
Week 4	0.39	0.43
Week 8	0.91	0.31
Week 12/end of study	1.21	0.08
Systolic blood pressure (mmHg)		
Week 4	-0.20	1.77
Week 8	0.50	1.70
Week 12/end of study	2.02	3.35
Weight (kg)		
Week 4	-0.34	0.83
Week 8	-0.53	-0.30
Week 12/end of study	-0.16	0.30

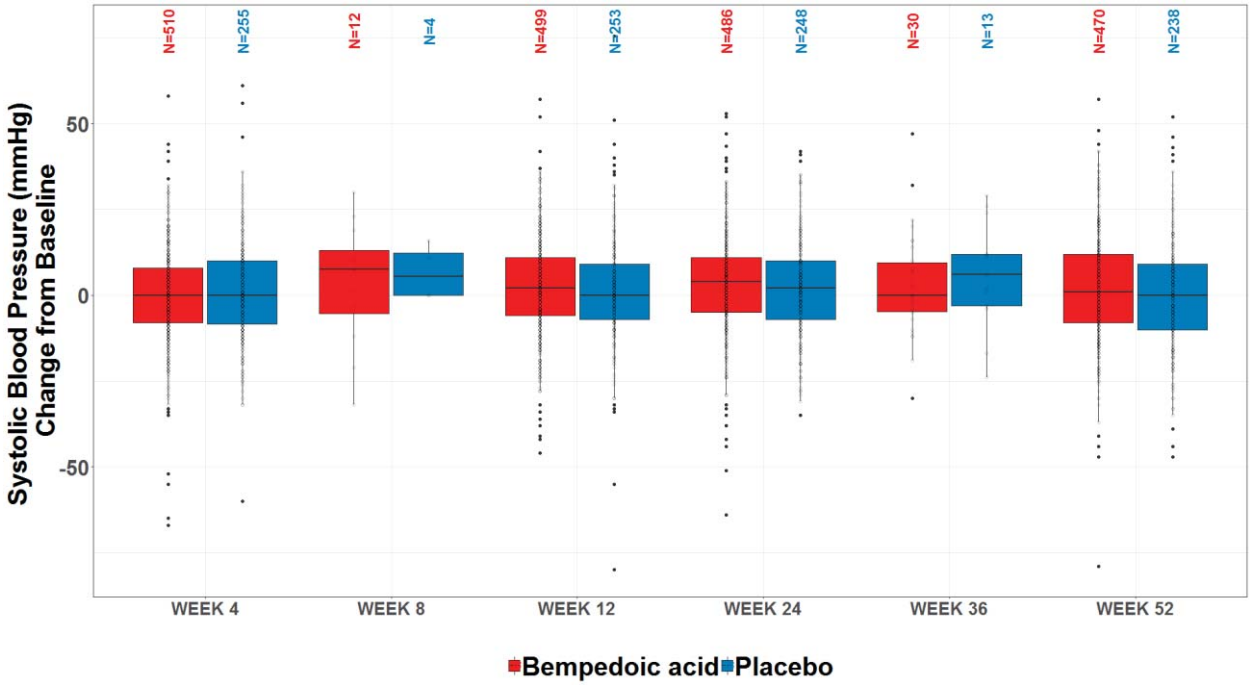
Source: advs.xpt; Software: Python
Abbreviations: N, number of subjects in group

Figure 49. Box Plot of Systolic Blood Pressure Change From Baseline Over Time, Safety Population, Trial 040



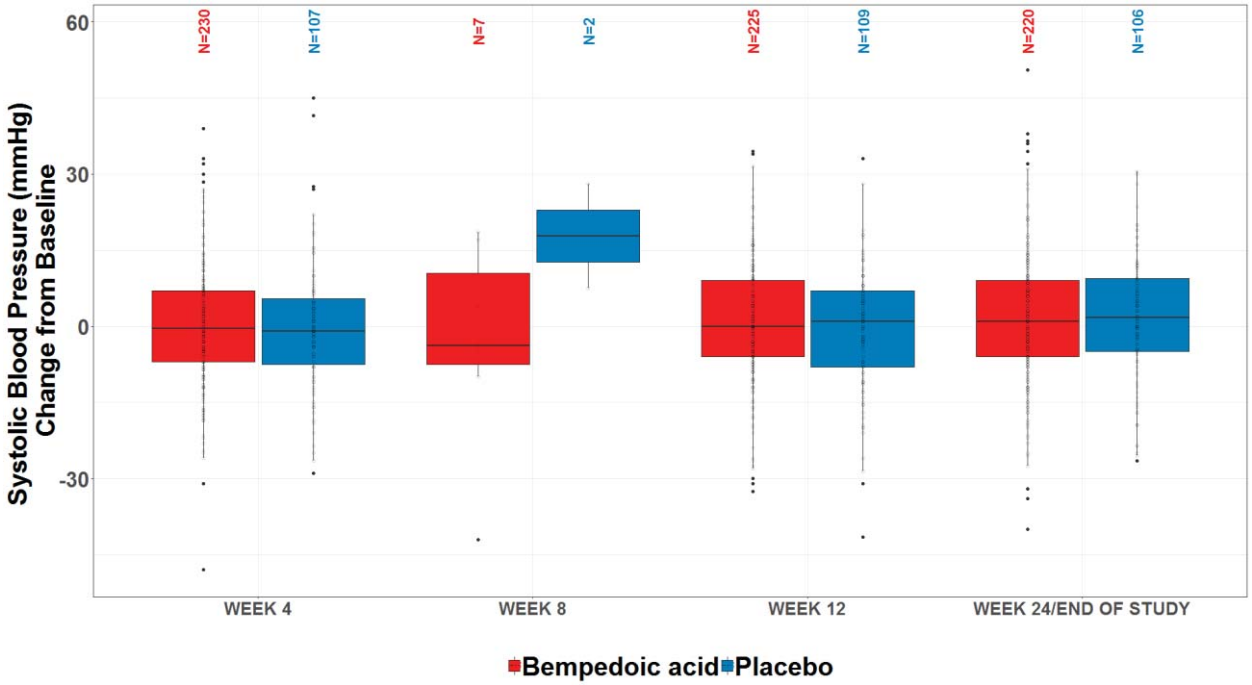
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 50. Box Plot of Systolic Blood Pressure Change From Baseline Over Time, Safety Population, Trial 047



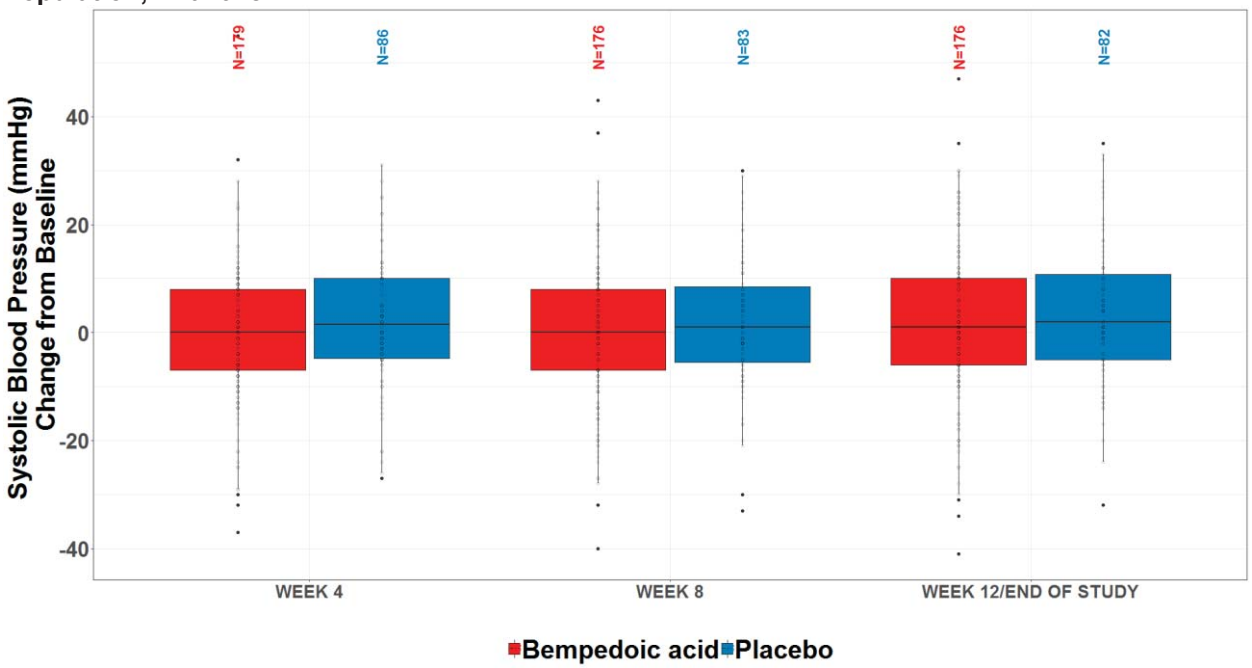
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 51. Box Plot of Systolic Blood Pressure Change From Baseline Over Time, Safety Population, Trial 046



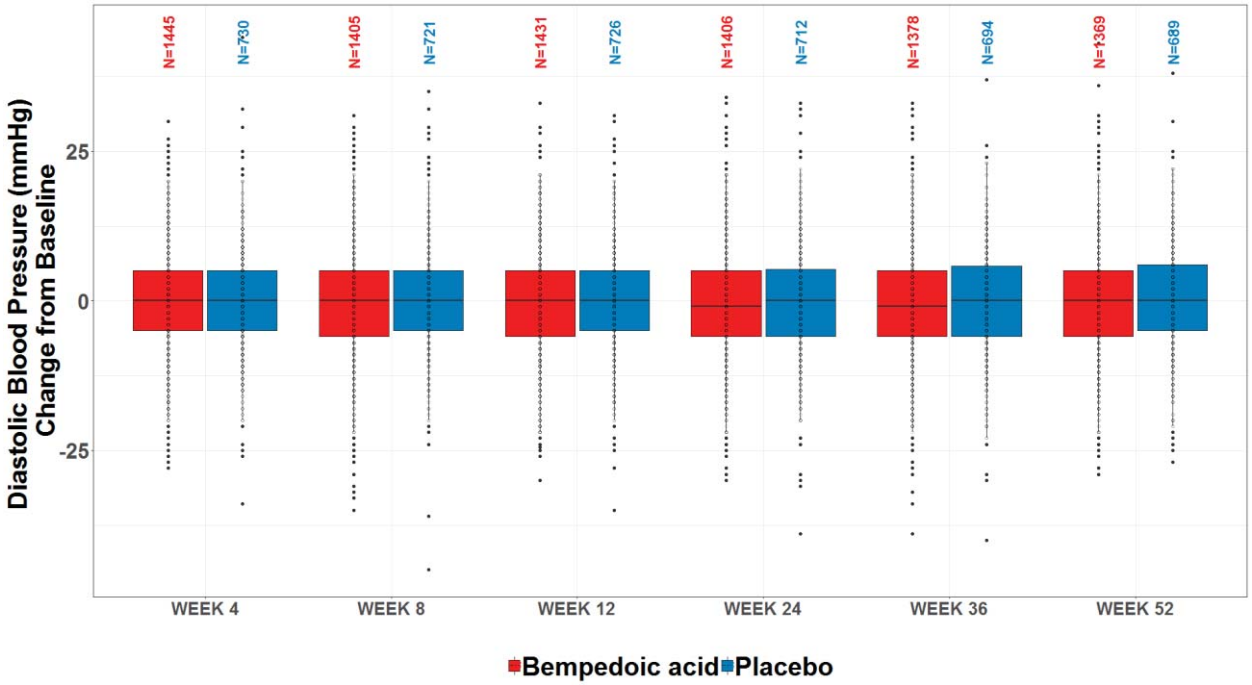
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 52. Box Plot of Systolic Blood Pressure Change From Baseline Over Time, Safety Population, Trial 048



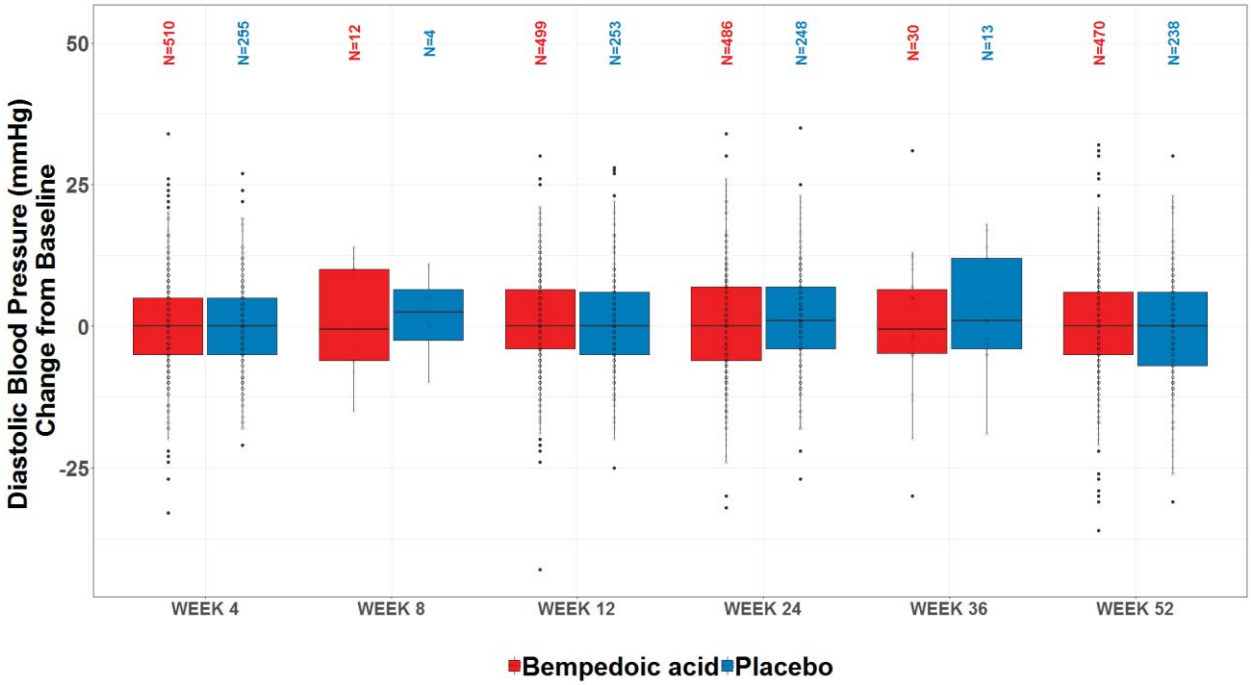
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 53. Box Plot of Diastolic Blood Pressure Change From Baseline Over Time, Safety Population, Trial 040



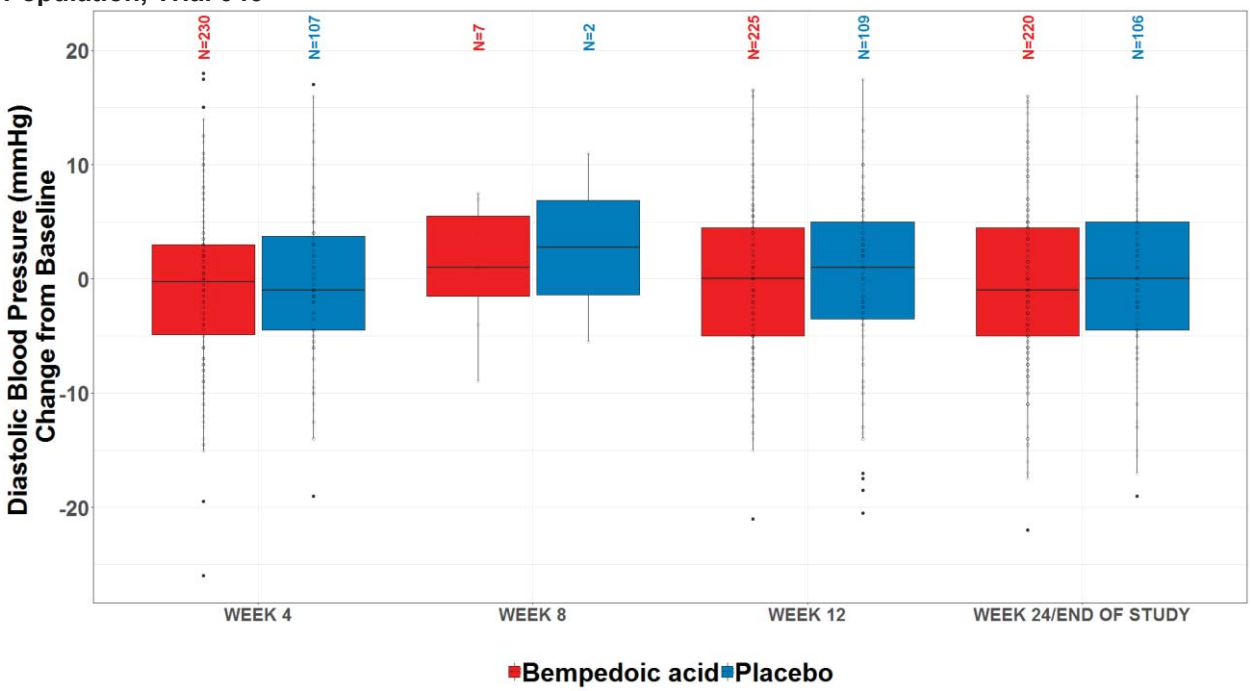
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 54. Box Plot of Diastolic Blood Pressure Change From Baseline Over Time, Safety Population, Trial 047



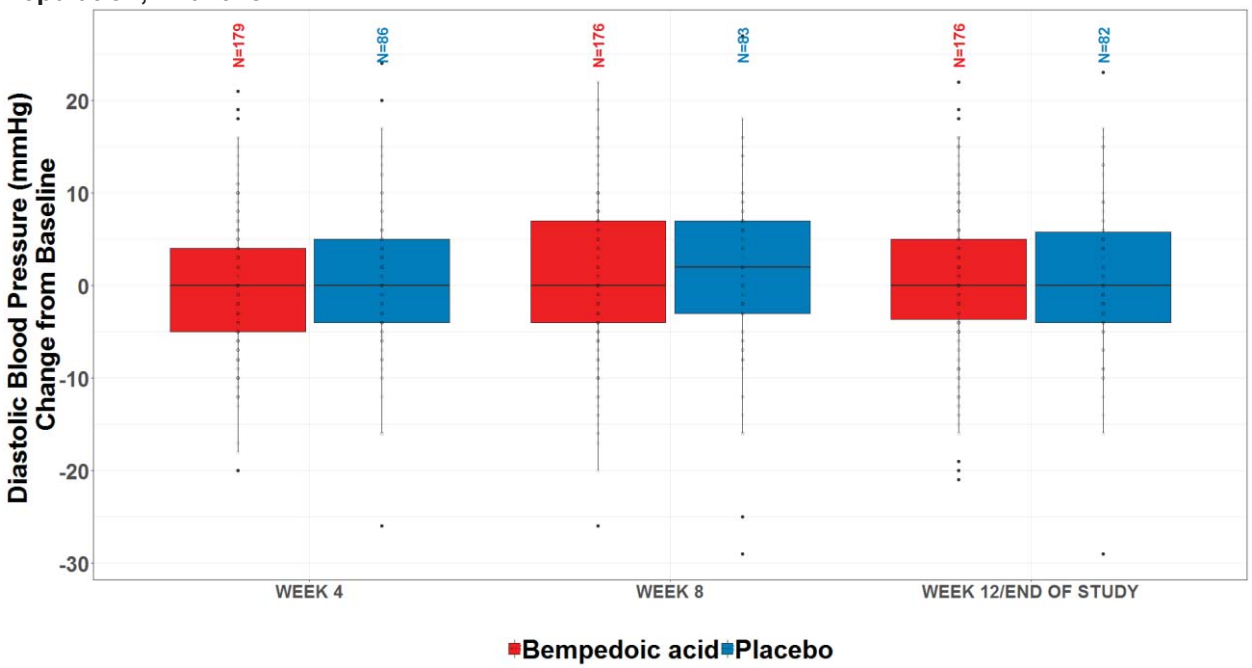
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 55. Box Plot of Diastolic Blood Pressure Change From Baseline Over Time, Safety Population, Trial 046



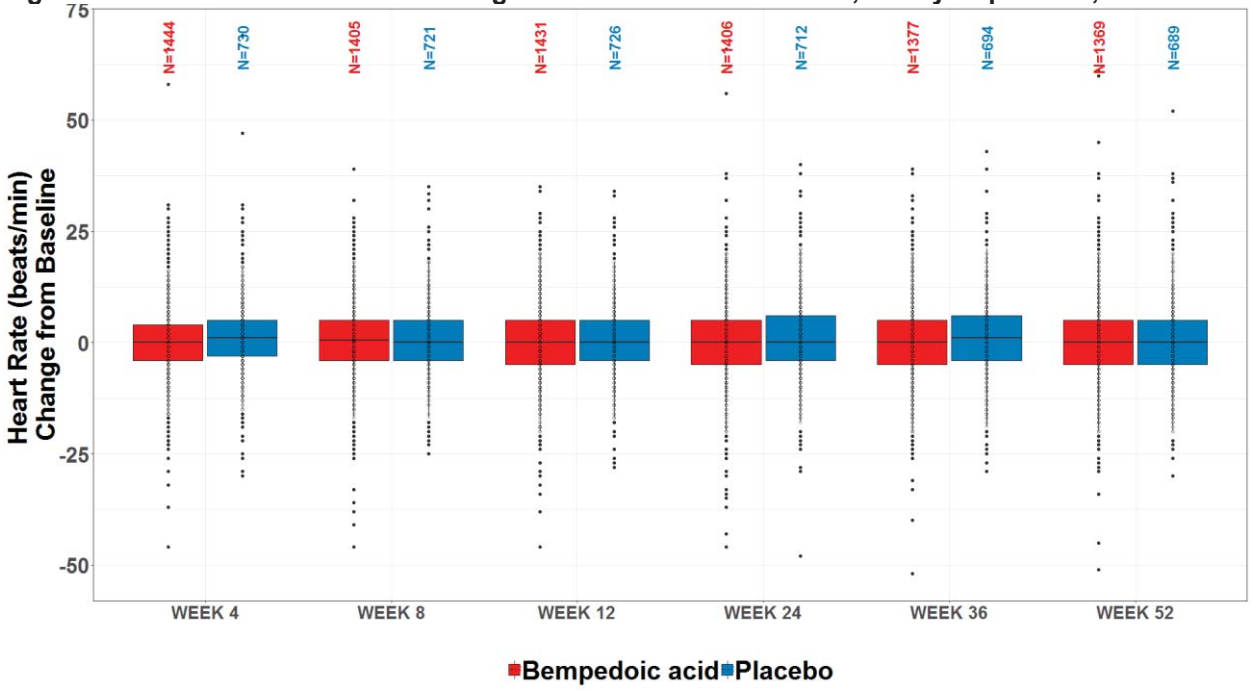
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 56. Box Plot of Diastolic Blood Pressure Change From Baseline Over Time, Safety Population, Trial 048



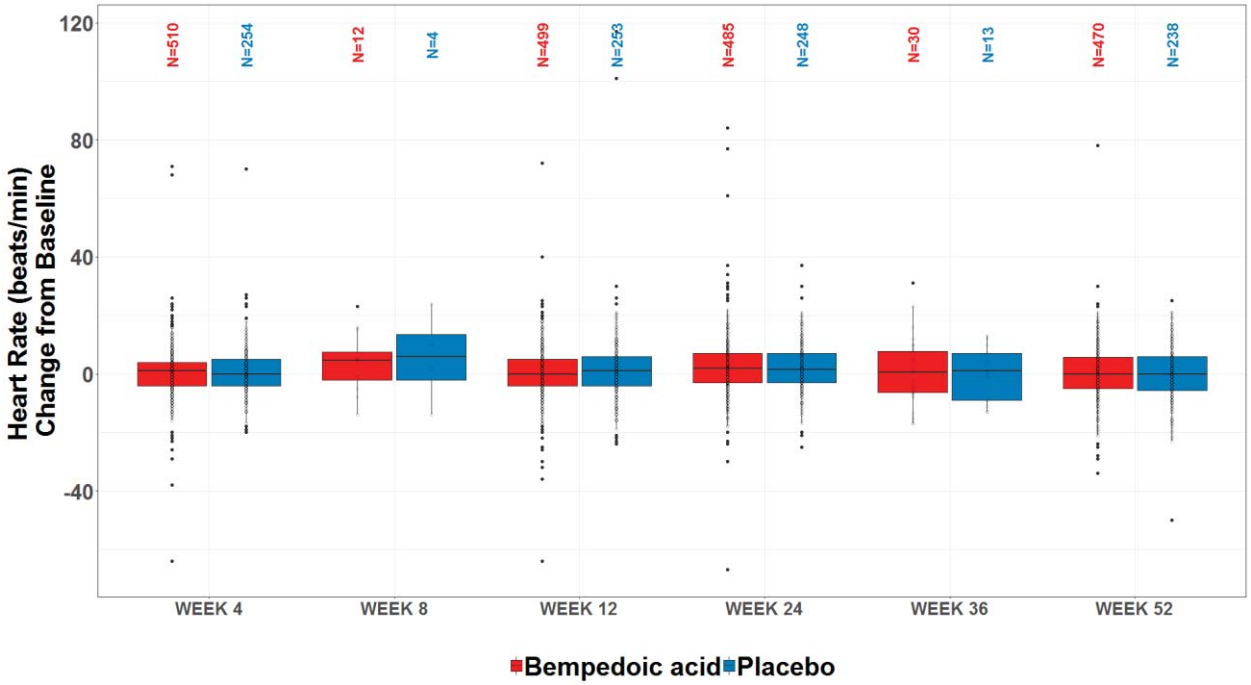
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 57. Box Plot of Heart Rate Change From Baseline Over Time, Safety Population, Trial 040



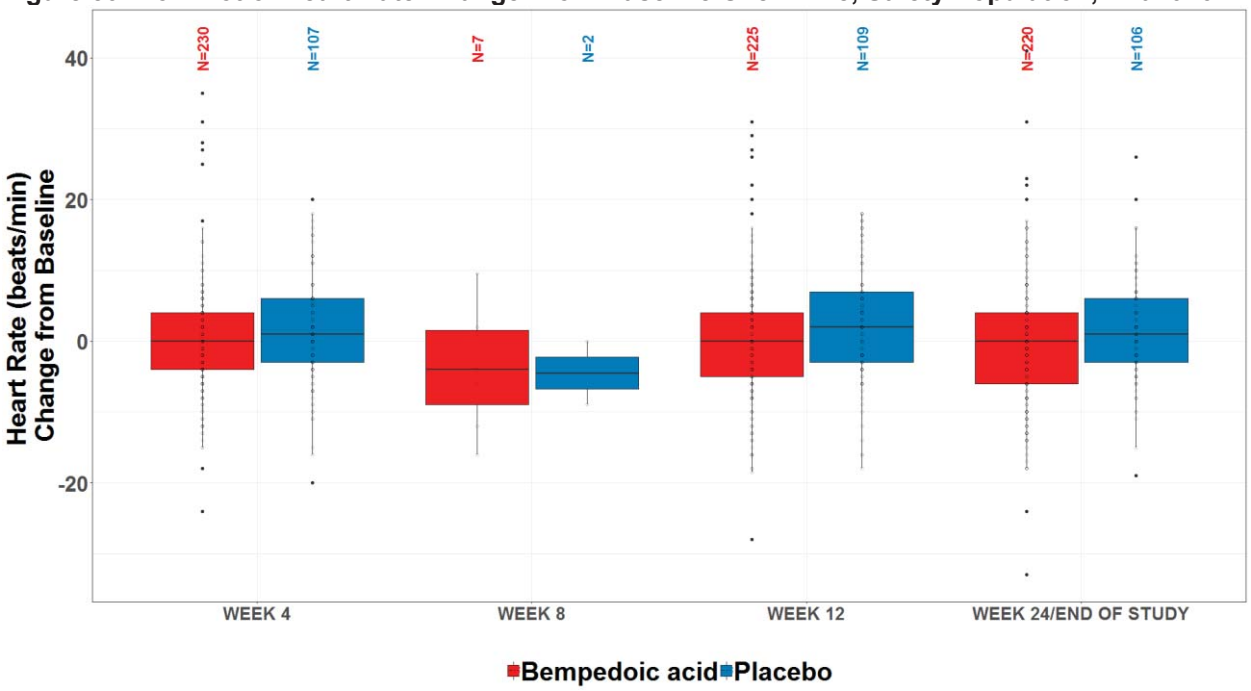
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 58. Box Plot of Heart Rate Change From Baseline Over Time, Safety Population, Trial 047



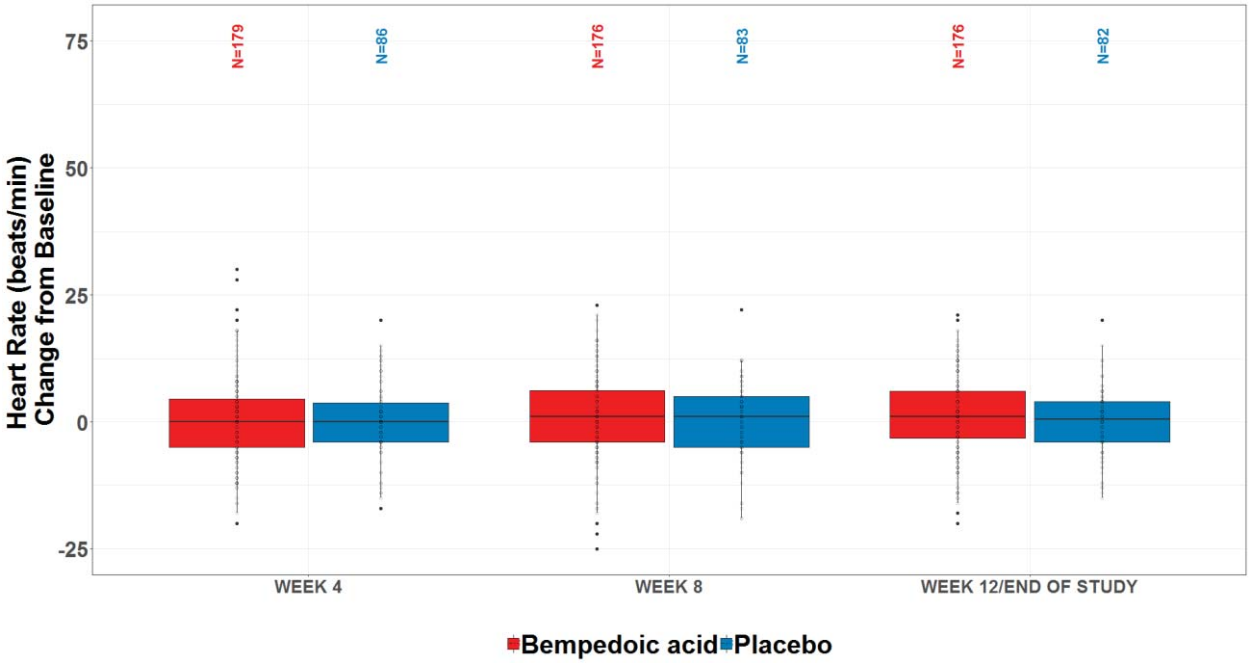
Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 59. Box Plot of Heart Rate Change From Baseline Over Time, Safety Population, Trial 046



Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

Figure 60. Box Plot of Heart Rate Change From Baseline Over Time, Safety Population, Trial 048



Source: ADVS; Software: Python
Abbreviations: N, number of subjects in group

17.1.3. ECGs

Table 127. Patients Meeting ECG Abnormality Criteria, From Baseline Through Week 52 (High CV Risk Pool) and Week 12 to 24 (No/Low Statin Pool), Safety Population

	High CV Risk Pool		No/Low Statin Pool	
ECG Analysis[1]	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Bempedoic Acid N=415 n (%)	Placebo N=198 n (%)
Normal to abnormal	194 (9.7)	114 (11.4)	56 (13.5)	31 (15.7)
Clinically significant (CS)	5 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Not clinically significant (NCS)	189 (9.4)	114 (11.4)	56 (13.5)	31 (15.7)
Abnormal NCS to abnormal CS	15 (0.7)	5 (0.5)	0 (0.0)	1 (0.5)

Source: ADEG; Software: JMP
[1] Investigator interpretation
Abbreviations: CV, cardiovascular; ECG, electrocardiogram; N, number of subjects in group; n, number of subjects with given ECG result

Table 128. Clinically Significant ECG Abnormalities, From Baseline Through Week 52 (High CV Risk Pool) and Week 12 to 24 (No/Low Statin Pool), Safety Population

	High CV Risk Pool		No/Low Statin Pool	
ECG Analysis[1]	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Bempedoic Acid N=415 n (%)	Placebo N=198 n (%)
Number of patients	20 (1.0)	5 (0.5)	0 (0.0)	1 (0.5)
Number of ECG abnormalities[2]	21	7	0	1
Arrhythmias	4 (19.0)	1 (14.3)	0 (0.0)	0 (0.0)
Tachycardia	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
PVCs	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Atrial fibrillation	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular tachycardia	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)
Unspecified arrythmia	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Conduction abnormalities	5 (23.8)	4 (57.1)	0 (0.0)	0 (0.0)
Bundle branch block[3]	4 (19.0)	2 (28.6)	0 (0.0)	0 (0.0)
1st degree AV block	1 (4.8)	2 (28.6)	0 (0.0)	0 (0.0)
ST-T wave changes	5 (23.8)	2 (28.6)	0 (0.0)	0 (0.0)
ST segment depression	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
T wave inversions	1 (4.8)	2 (28.6)	0 (0.0)	0 (0.0)
Q wave	3 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	7 (33.3)	0 (0.0)	0 (0.0)	1 (100.0)

Source: ADEG; Software: JMP
[1] Investigator interpretation
[2] Includes all ECG abnormalities reported by investigator, may be >1 per patient3 LBBB, RBBB, LAFB
Abbreviations: AV, atrioventricular; CV, cardiovascular, ECG, electrocardiogram; N, number of subjects in group; n, number of subjects with given ECG result; PVC, premature ventricular contractions

17.1.4. Laboratory Tests

Only labs from Trial 040, the largest and longest phase 3 trial, are displayed. Lab results in Studies 047, 046, and 048 were consistent with the results provided.

Table 129. Selected Lab Parameters Change From Baseline Over Time, Safety Population, Trial 040

Laboratory Parameters	Bempedoic Acid (N=1487) n (%)					Placebo (N=742) n (%)					Difference of Mean CFB
Week	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	
Alanine aminotransferase (U/L) CN unit											
Baseline	1487	24.9 (12.9)	22	0 (0)	0	742	24.6 (11.3)	22	0 (0)	0	0
Week 4	1440	27.3 (18.3)	23	2.4 (16)	1	729	25.8 (14.3)	22	1.2 (10.5)	0	1.2
Week 8	1402	27.4 (15.7)	23	2.4 (13.1)	2	720	25.2 (12.7)	22	0.6 (9.1)	0	1.8
Week 12	1426	27.8 (15.8)	24	2.8 (13.3)	1	726	26.1 (13.3)	23	1.3 (10.4)	1	1.5
Week 24	1401	26.9 (17.7)	23	1.9 (15.4)	1	708	26.4 (27.2)	22	1.9 (26)	0	0
Week 36	1375	25.5 (14.7)	22	0.2 (13.1)	0	693	25.6 (21.8)	22	0.9 (20.4)	0	-0.7
Week 52	1365	25.2 (15.5)	21	0.2 (13.9)	0	685	24.8 (12.5)	22	0.1 (10)	0	0.1
Albumin (g/dL) CN unit											
Baseline	1487	4.3 (0.3)	4.3	0 (0)	0	742	4.3 (0.2)	4.3	0 (0)	0	0
Week 4	1440	4.4 (0.3)	4.4	0.1 (0.2)	0.1	729	4.3 (0.2)	4.3	0 (0.2)	0	0.1
Week 8	1402	4.4 (0.3)	4.4	0.1 (0.2)	0.1	720	4.3 (0.2)	4.3	0 (0.2)	0	0.1
Week 12	1427	4.4 (0.3)	4.4	0.1 (0.2)	0.1	726	4.3 (0.2)	4.3	0 (0.2)	0	0.1
Week 24	1402	4.4 (0.3)	4.4	0.1 (0.2)	0.1	709	4.3 (0.2)	4.3	0 (0.2)	0	0.1
Week 36	1376	4.3 (0.3)	4.3	0 (0.2)	0	693	4.2 (0.2)	4.2	0 (0.2)	0	0
Week 52	1365	4.3 (0.3)	4.3	0 (0.2)	0	685	4.2 (0.2)	4.2	-0.1 (0.2)	-0.1	0.1
Alkaline phosphatase (U/L) CN unit											
Baseline	1487	77.6 (23.1)	74	0 (0)	0	742	78.4 (22.1)	76	0 (0)	0	0
Week 4	1440	63.9 (19.8)	61	-13.5 (11.6)	-13	729	78.2 (24)	76	0 (11.6)	-1	-13.5
Week 8	1402	63.1 (22.5)	60	-14.1 (15.7)	-14	720	78.2 (23.5)	75	-0.1 (9.4)	-1	-14
Week 12	1427	63.8 (19.7)	61	-13.3 (13.4)	-13	726	79.2 (23.6)	76	0.8 (10)	0	-14.1
Week 24	1402	64.4 (20.1)	61	-12.8 (15.4)	-12	709	80.2 (32.6)	76	1.8 (22.3)	0	-14.6
Week 36	1376	62.7 (20.4)	60	-14.3 (15.6)	-14	693	77.8 (25.3)	74	-0.5 (13.9)	-2	-13.8
Week 52	1365	64 (21.4)	61	-13.1 (16.5)	-13	685	78.6 (24.1)	75	0.4 (12.5)	0	-13.5

Laboratory Parameters	Bempedoic Acid (N=1487) n (%)					Placebo (N=742) n (%)					Difference of Mean CFB
Week	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	
Aspartate aminotransferase (U/L) CN unit											
Baseline	1487	22.8 (8.2)	21	0 (0)	0	742	22.8 (7.5)	21	0 (0)	0	0
Week 4	1435	29.1 (26.6)	25	6.2 (26.1)	4	728	24.3 (9.1)	22	1.4 (7.1)	1	4.8
Week 8	1398	28.6 (11)	26	5.6 (9.8)	4	719	24.2 (9.6)	22	1.3 (7.9)	1	4.3
Week 12	1426	28.4 (14.8)	25	5.6 (13.9)	4	724	24 (9.6)	22	1 (7.7)	0	4.6
Week 24	1401	27.8 (16.5)	25	5 (15.5)	3	707	24.2 (20.8)	21	1.4 (19.8)	0	3.6
Week 36	1370	27.6 (12.6)	25	4.5 (11.4)	3	693	24.5 (18.7)	22	1.7 (17.8)	1	2.8
Week 52	1360	26.6 (13.5)	24	3.7 (12.7)	2	680	23.3 (8.4)	21	0.6 (7)	0	3.1
Bilirubin (mg/dL) CN unit											
Baseline	1487	0.7 (0.3)	0.6	0 (0)	0	742	0.6 (0.3)	0.6	0 (0)	0	0
Week 4	1440	0.6 (0.2)	0.6	-0.1 (0.2)	0	729	0.6 (0.3)	0.6	0 (0.2)	0	-0.1
Week 8	1402	0.6 (0.2)	0.6	-0.1 (0.2)	0	720	0.6 (0.3)	0.6	0 (0.2)	0	-0.1
Week 12	1426	0.6 (0.2)	0.6	-0.1 (0.2)	0	726	0.6 (0.3)	0.6	0 (0.2)	0	-0.1
Week 24	1401	0.6 (0.2)	0.6	-0.1 (0.2)	0	708	0.6 (0.3)	0.6	0 (0.2)	0	-0.1
Week 36	1375	0.6 (0.2)	0.6	-0.1 (0.2)	0	693	0.7 (0.3)	0.6	0 (0.2)	0	-0.1
Week 52	1365	0.6 (0.2)	0.6	0 (0.2)	0	685	0.7 (0.3)	0.6	0 (0.2)	0	0
Blood urea nitrogen (mg/dL) CN unit											
Baseline	1487	16.9 (5.2)	16	0 (0)	0	742	16.8 (4.8)	16	0 (0)	0	0
Week 4	1440	18.8 (6)	18	1.9 (3.9)	2	729	16.7 (4.7)	16	-0.1 (3.6)	0	2
Week 8	1402	18.7 (6.1)	18	1.8 (4.2)	2	720	17 (4.8)	16	0.2 (3.6)	0	1.6
Week 12	1427	18.7 (6.1)	18	1.7 (4.1)	2	726	17 (5)	17	0.2 (3.7)	0	1.5
Week 24	1402	18.8 (6.2)	18	1.8 (4.4)	2	709	17.2 (5.1)	17	0.4 (3.9)	0	1.4
Week 36	1376	18.5 (5.9)	18	1.6 (4.4)	1	693	17.1 (5.3)	16	0.4 (4.1)	0	1.2
Week 52	1365	18.6 (6.4)	17	1.7 (4.6)	1	685	17 (5.4)	16	0.1 (4.3)	0	1.6
Calcium (mg/dL) CN unit											
Baseline	1487	9.4 (0.4)	9.4	0 (0)	0	742	9.4 (0.4)	9.3	0 (0)	0	0
Week 4	1440	9.5 (0.4)	9.4	0.1 (0.4)	0.1	729	9.4 (0.4)	9.4	0 (0.4)	0	0.1
Week 8	1402	9.5 (0.4)	9.4	0.1 (0.3)	0.1	720	9.4 (0.4)	9.3	0 (0.4)	0	0.1
Week 12	1427	9.5 (0.4)	9.4	0.1 (0.3)	0.1	726	9.4 (0.4)	9.4	0 (0.4)	0	0.1
Week 24	1402	9.5 (0.4)	9.4	0.1 (0.4)	0.1	709	9.4 (0.4)	9.4	0 (0.4)	0	0.1
Week 36	1376	9.4 (0.4)	9.4	0 (0.4)	0	693	9.3 (0.4)	9.3	-0.1 (0.4)	-0.1	0.1
Week 52	1365	9.4 (0.4)	9.4	0 (0.4)	0	685	9.3 (0.4)	9.3	-0.1 (0.4)	-0.1	0.1

Laboratory Parameters	Bempedoic Acid (N=1487) n (%)					Placebo (N=742) n (%)					Difference of Mean CFB
Week	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	
Carbon dioxide (mEq/L) CN unit											
Baseline	1487	22.9 (2.3)	23	0 (0)	0	742	22.7 (2.4)	23	0 (0)	0	0
Week 4	1440	23 (2.2)	23	0.2 (2.3)	0	729	22.9 (2.3)	23	0.2 (2.3)	0	0
Week 8	1402	23 (2.2)	23	0.1 (2.2)	0	720	22.8 (2.1)	23	0.2 (2.3)	0	-0.1
Week 12	1427	22.4 (2.3)	22	-0.5 (2.5)	0	726	22.3 (2.3)	22	-0.4 (2.5)	0	-0.1
Week 24	1402	22.3 (2.3)	22	-0.6 (2.5)	-1	709	22.1 (2.3)	22	-0.5 (2.5)	-1	-0.1
Week 36	1376	22.9 (2.2)	23	0 (2.3)	0	693	22.8 (2.2)	23	0.1 (2.4)	0	-0.1
Week 52	1365	22.7 (2.1)	23	-0.2 (2.3)	0	685	22.7 (2.2)	23	0 (2.4)	0	-0.2
Chloride (mmol/L) CN unit											
Baseline	1487	105.4 (2.8)	106	0 (0)	0	742	105.5 (2.7)	106	0 (0)	0	0
Week 4	1440	105.3 (2.7)	105	-0.1 (2.3)	0	729	105.4 (2.9)	105	-0.1 (2.3)	0	0
Week 8	1402	105.4 (2.7)	106	0 (2.2)	0	720	105.5 (3)	106	-0.1 (2.5)	0	0.1
Week 12	1427	105.4 (2.7)	106	0 (2.3)	0	726	105.7 (2.8)	106	0.1 (2.4)	0	-0.1
Week 24	1402	105.7 (2.7)	106	0.2 (2.5)	0	709	105.8 (2.8)	106	0.2 (2.5)	0	0
Week 36	1376	105.6 (2.6)	106	0.1 (2.5)	0	693	105.5 (2.8)	106	0 (2.5)	0	0.1
Week 52	1365	105.3 (2.6)	105	-0.2 (2.4)	0	685	105.4 (2.8)	106	-0.2 (2.5)	0	0
Creatine kinase (U/L) CN unit											
Baseline	1487	136.4 (116.8)	108	0 (0)	0	742	131.4 (92.7)	108.5	0 (0)	0	0
Week 4	1440	170.2 (569.9)	110	28.4 (572.5)	0	729	133.5 (154.8)	106	-0.2 (156.4)	-1	28.6
Week 8	1402	137.4 (97.4)	110	-0.1 (114.2)	1	720	139.7 (201.8)	106	8.3 (200.6)	-1	-8.4
Week 12	1426	154.6 (347.8)	111	16 (349.7)	2	726	136.9 (126.8)	107	3.9 (129.3)	0	12.1
Week 24	1401	157 (237.8)	113	19.4 (242.6)	3.5	708	132.3 (91.8)	109	-4.3 (116.9)	-1	23.7
Week 36	1375	142.2 (108.8)	114	3 (120)	2	693	135.4 (92.5)	109	1.6 (92.1)	2	1.4
Week 52	1365	135.7 (113.1)	106	-0.3 (109.4)	-3	685	126.9 (85.8)	104	-3.8 (88.7)	-3.5	3.5
Creatinine (mg/dL) CN unit											
Baseline	1487	1 (0.2)	1	0 (0)	0	742	1 (0.2)	0.9	0 (0)	0	0
Week 4	1440	1 (0.2)	1	0.1 (0.1)	0	729	1 (0.2)	0.9	0 (0.1)	0	0.1
Week 8	1402	1 (0.3)	1	0.1 (0.1)	0	720	1 (0.2)	0.9	0 (0.1)	0	0.1
Week 12	1427	1 (0.3)	1	0 (0.1)	0	726	1 (0.2)	0.9	0 (0.1)	0	0
Week 24	1402	1 (0.2)	1	0 (0.1)	0	709	1 (0.2)	0.9	0 (0.1)	0	0
Week 36	1376	1 (0.2)	1	0 (0.1)	0	693	1 (0.2)	0.9	0 (0.1)	0	0
Week 52	1343	1 (0.3)	0.9	0 (0.1)	0	677	0.9 (0.2)	0.9	0 (0.1)	0	0

Laboratory Parameters	Bempedoic Acid (N=1487) n (%)					Placebo (N=742) n (%)					Difference of Mean CFB
Week	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	
Direct bilirubin (mg/dL) CN unit											
Baseline	1222	0.3 (0.1)	0.2	0 (0)	0	624	0.3 (0.1)	0.2	0 (0)	0	0
Week 4	983	0.3 (0.1)	0.2	0 (0.1)	0	517	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 8	834	0.3 (0.1)	0.2	0 (0.1)	0	449	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 12	740	0.3 (0.1)	0.2	0 (0.1)	0	381	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 24	374	0.2 (0.1)	0.2	0 (0.1)	0	190	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 36	229	0.3 (0.1)	0.2	0 (0.1)	0	114	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 52	59	0.2 (0.1)	0.2	0 (0.1)	0	30	0.2 (0.1)	0.2	0 (0.1)	0	0
Glomerular filtration rate, estimated (mL/min/1.73m2) CN unit											
Baseline	1487	77.5 (18.3)	76	0 (0)	0	742	77.4 (17.1)	76	0 (0)	0	0
Week 4	1435	72 (18.3)	71	-5.4 (9)	-5	728	76.1 (17.3)	76	-1.3 (8.8)	-1	-4.1
Week 8	1401	72.1 (18.3)	71	-5.2 (9.1)	-5	720	75.7 (17.3)	75	-1.8 (9.1)	-2	-3.4
Week 12	1427	72.8 (18.7)	72	-4.5 (9)	-5	726	76.2 (16.9)	76	-1.2 (8.9)	-1	-3.3
Week 24	1403	74 (19)	73	-3.4 (9.4)	-4	709	76.8 (17.2)	76	-0.4 (8.9)	0	-3
Week 36	1375	74.3 (19.1)	73	-3.1 (9.8)	-3	693	77.3 (17.9)	76	-0.1 (9.6)	0	-3
Week 52	1344	75.5 (19.9)	75	-1.9 (10.3)	-2	676	78.4 (18.5)	77	1.1 (10.2)	1	-3
Glucose (mg/dL) CN unit											
Baseline	1487	107.7 (26.6)	101	0 (0)	0	742	107.7 (27.4)	100	0 (0)	0	0
Week 4	1437	109.6 (27.6)	102	2.3 (19.2)	2	727	112.5 (34.2)	103	5 (25.1)	3	-2.7
Week 8	1401	109.8 (26.6)	103	2.4 (19.7)	2	717	112.8 (38.5)	104	5.2 (30.5)	3	-2.8
Week 12	1425	108.5 (27.3)	101	0.6 (19.5)	1	726	109.9 (28.8)	102	2 (23.4)	2	-1.4
Week 24	1399	109.6 (31.1)	101	1.4 (22.2)	0	707	110 (29.8)	102	1.9 (24.1)	1	-0.5
Week 36	1373	108.9 (29.7)	101	1.4 (21.7)	1	689	111.6 (32.6)	102	3.4 (26)	2	-2
Week 52	1360	107.2 (30.6)	100	-0.3 (23.7)	-1	681	109.4 (32.4)	101	1.7 (23.6)	0	-2
Lactate dehydrogenase (U/L) CN unit											
Baseline	1487	180.2 (36.2)	177	0 (0)	0	742	180.6 (34.6)	176.5	0 (0)	0	0
Week 4	1426	179 (42.4)	174	-1.3 (28.1)	-3	725	176.9 (33.6)	173	-3.6 (20.7)	-4	2.3
Week 8	1393	176.5 (35.3)	172	-3.8 (23)	-4	714	178.3 (40.2)	174	-2.7 (28.1)	-3	-1.1
Week 12	1421	180.2 (38.6)	176	0.1 (26.4)	-1	721	181 (37.2)	176	0.6 (21.9)	-1	-0.5
Week 24	1397	180.6 (37)	176	0.5 (23.5)	0	704	181.7 (36.1)	176	1.3 (23.2)	1	-0.8
Week 36	1366	178.5 (36.3)	173	-1.5 (23.4)	-2	683	180.5 (40.5)	176	-0.4 (28.1)	-1	-1.1
Week 52	1352	178.3 (36.6)	175	-1.6 (22.7)	-1	675	179.8 (37.2)	175	-0.3 (25.2)	-2	-1.3

Laboratory Parameters	Bempedoic Acid (N=1487) n (%)					Placebo (N=742) n (%)					Difference of Mean CFB
Week	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	
Phosphate (mg/dL) CN unit											
Baseline	1487	3.4 (0.5)	3.4	0 (0)	0	742	3.5 (0.5)	3.4	0 (0)	0	0
Week 4	1440	3.4 (0.6)	3.3	-0.1 (0.5)	-0.1	729	3.5 (0.5)	3.5	0 (0.4)	0	-0.1
Week 8	1402	3.4 (0.5)	3.3	-0.1 (0.4)	-0.1	720	3.5 (0.6)	3.5	0 (0.6)	0	-0.1
Week 12	1427	3.3 (0.5)	3.3	-0.1 (0.4)	-0.1	726	3.4 (0.5)	3.4	0 (0.4)	0	-0.1
Week 24	1402	3.4 (0.5)	3.3	-0.1 (0.4)	-0.1	709	3.5 (0.5)	3.5	0 (0.4)	0	-0.1
Week 36	1375	3.4 (0.5)	3.3	-0.1 (0.5)	-0.1	693	3.4 (0.5)	3.4	0 (0.4)	0	-0.1
Week 52	1365	3.3 (0.5)	3.3	-0.1 (0.4)	-0.1	685	3.4 (0.5)	3.4	0 (0.5)	0	-0.1
Potassium (mmol/L) CN unit											
Baseline	1487	4.4 (0.4)	4.4	0 (0)	0	742	4.4 (0.4)	4.4	0 (0)	0	0
Week 4	1439	4.5 (0.4)	4.5	0.1 (0.4)	0.1	729	4.5 (0.4)	4.4	0.1 (0.4)	0	0
Week 8	1400	4.5 (0.4)	4.5	0.1 (0.4)	0.1	720	4.5 (0.4)	4.4	0 (0.4)	0	0.1
Week 12	1427	4.5 (0.4)	4.5	0.1 (0.4)	0.1	726	4.4 (0.4)	4.4	0 (0.4)	0	0.1
Week 24	1402	4.5 (0.4)	4.5	0.1 (0.4)	0	709	4.4 (0.4)	4.4	0 (0.4)	0	0.1
Week 36	1375	4.5 (0.4)	4.5	0.1 (0.4)	0.1	693	4.5 (0.4)	4.5	0.1 (0.4)	0	0
Week 52	1365	4.5 (0.4)	4.4	0 (0.4)	0	685	4.4 (0.4)	4.4	0 (0.4)	0	0
Sodium (mmol/L) CN unit											
Baseline	1487	140.3 (2.1)	140	0 (0)	0	742	140.2 (2.1)	140	0 (0)	0	0
Week 4	1440	140.3 (2.2)	140	0 (2)	0	729	140 (2.4)	140	-0.2 (2.1)	0	0.2
Week 8	1402	140.4 (2.2)	140	0.1 (2)	0	720	140.1 (2.4)	140	-0.1 (2.2)	0	0.2
Week 12	1427	140.5 (2.2)	141	0.2 (2)	0	726	140.4 (2.4)	140	0.2 (2)	0	0
Week 24	1402	140.7 (2.2)	141	0.3 (2)	0	709	140.4 (2.2)	141	0.2 (2)	0	0.1
Week 36	1376	140.5 (2.2)	141	0.1 (2)	0	693	140.3 (2.3)	140	0.1 (2)	0	0
Week 52	1365	140.6 (2.2)	141	0.3 (2)	0	685	140.4 (2.4)	141	0.2 (2.1)	0	0.1
Urate (mg/dL) CN unit											
Baseline	1487	6.1 (1.4)	6	0 (0)	0	742	6 (1.3)	6	0 (0)	0	0
Week 4	1440	6.8 (1.5)	6.8	0.8 (0.8)	0.7	729	6 (1.3)	5.9	0 (0.6)	0	0.8
Week 8	1402	6.9 (1.5)	6.8	0.8 (0.9)	0.8	720	6 (1.4)	6	0 (0.7)	0.1	0.8
Week 12	1427	6.9 (1.5)	6.8	0.8 (0.9)	0.8	726	6 (1.4)	6	0 (0.7)	0	0.8
Week 24	1402	6.9 (1.6)	6.8	0.8 (1)	0.8	709	6 (1.4)	6	0 (0.8)	0	0.8
Week 36	1376	6.9 (1.5)	6.9	0.8 (1.1)	0.9	693	6 (1.3)	6	0 (0.8)	0	0.8
Week 52	1365	6.8 (1.6)	6.7	0.7 (1.1)	0.7	685	5.9 (1.4)	5.8	-0.1 (0.9)	-0.1	0.8

Laboratory Parameters	Bempedoic Acid (N=1487) n (%)					Placebo (N=742) n (%)					Difference of Mean CFB
Week	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	
Basophils (10^9/L) CN unit											
Baseline	1487	0 (0)	0	0 (0)	0	742	0 (0)	0	0 (0)	0	0
Week 4	1433	0 (0)	0	0 (0)	0	726	0.1 (0)	0	0 (0)	0	0
Week 8	1397	0 (0)	0	0 (0)	0	718	0 (0)	0	0 (0)	0	0
Week 12	1424	0.1 (0)	0	0 (0)	0	718	0 (0)	0	0 (0)	0	0
Week 24	1396	0.1 (0)	0	0 (0)	0	707	0.1 (0)	0	0 (0)	0	0
Week 36	1370	0 (0)	0	0 (0)	0	685	0.1 (0)	0	0 (0)	0	0
Week 52	1344	0 (0)	0	0 (0)	0	673	0 (0)	0	0 (0)	0	0
Eosinophils (10^9/L) CN unit											
Baseline	1487	0.2 (0.1)	0.2	0 (0)	0	742	0.2 (0.1)	0.2	0 (0)	0	0
Week 4	1433	0.2 (0.1)	0.2	0 (0.1)	0	726	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 8	1397	0.2 (0.2)	0.2	0 (0.1)	0	718	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 12	1424	0.2 (0.2)	0.2	0 (0.1)	0	718	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 24	1396	0.2 (0.1)	0.2	0 (0.1)	0	707	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 36	1370	0.2 (0.2)	0.2	0 (0.1)	0	685	0.2 (0.1)	0.2	0 (0.1)	0	0
Week 52	1344	0.2 (0.1)	0.2	0 (0.1)	0	673	0.2 (0.1)	0.2	0 (0.1)	0	0
Ery. mean corpuscular volume (fL) CN unit											
Baseline	1487	93.9 (4.8)	93.8	0 (0)	0	742	93.8 (5)	93.5	0 (0)	0	0
Week 4	1433	93.7 (4.8)	93.7	-0.1 (2.2)	-0.2	726	94 (5.1)	93.8	0.3 (2.2)	0.3	-0.4
Week 8	1398	93.9 (4.8)	93.8	0 (2.4)	-0.1	718	94.1 (5)	93.9	0.3 (2.6)	0.3	-0.3
Week 12	1424	94.2 (4.8)	94.1	0.3 (2.7)	0.3	718	94 (4.9)	94	0.3 (2.7)	0.3	0
Week 24	1396	95.4 (5.1)	95.2	1.6 (3.6)	1.7	707	95.3 (5.3)	95.1	1.6 (3.7)	1.7	0
Week 36	1370	95.9 (4.9)	95.9	2.1 (3.3)	2.1	685	95.8 (5.3)	95.8	2.2 (3.6)	2.2	-0.1
Week 52	1344	94.8 (4.8)	94.8	1 (2.9)	1	673	94.8 (5.1)	94.6	1.2 (3)	1.2	-0.2
Erythrocytes (10^12/L) CN unit											
Baseline	1487	4.7 (0.4)	4.7	0 (0)	0	742	4.7 (0.4)	4.7	0 (0)	0	0
Week 4	1433	4.6 (0.4)	4.6	-0.1 (0.2)	-0.1	726	4.6 (0.4)	4.7	0 (0.2)	0	-0.1
Week 8	1398	4.6 (0.4)	4.6	-0.1 (0.2)	-0.1	718	4.7 (0.4)	4.7	0 (0.2)	0	-0.1
Week 12	1424	4.6 (0.4)	4.6	-0.1 (0.2)	-0.1	718	4.7 (0.4)	4.7	0 (0.2)	0	-0.1
Week 24	1396	4.6 (0.4)	4.6	-0.1 (0.3)	-0.1	707	4.6 (0.4)	4.7	0 (0.2)	0	-0.1
Week 36	1370	4.5 (0.4)	4.5	-0.2 (0.3)	-0.2	685	4.6 (0.4)	4.6	-0.1 (0.2)	-0.1	-0.1
Week 52	1344	4.5 (0.4)	4.5	-0.2 (0.3)	-0.2	673	4.6 (0.4)	4.6	-0.1 (0.3)	-0.1	-0.1

Laboratory Parameters	Bempedoic Acid (N=1487) n (%)					Placebo (N=742) n (%)					Difference of Mean CFB
Week	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	
Hematocrit (%) CN unit											
Baseline	1487	44 (3.8)	44	0 (0)	0	742	43.5 (3.7)	43.5	0 (0)	0	0
Week 4	1433	43.1 (3.8)	43.1	-0.8 (2.1)	-0.9	726	43.5 (3.7)	43.7	0 (2.1)	0.1	-0.8
Week 8	1398	42.8 (3.8)	42.8	-1.2 (2.3)	-1.1	718	43.7 (3.7)	43.8	0.2 (2.3)	0.2	-1.4
Week 12	1424	42.9 (3.8)	43	-1.1 (2.5)	-1.1	718	43.8 (3.7)	43.8	0.2 (2.4)	0.3	-1.3
Week 24	1396	43.6 (3.9)	43.7	-0.4 (2.6)	-0.4	707	44.2 (4)	44.2	0.7 (2.6)	0.7	-1.1
Week 36	1370	43.3 (4)	43.4	-0.7 (2.7)	-0.6	685	44 (3.9)	44	0.5 (2.7)	0.6	-1.2
Week 52	1344	42.8 (4)	42.9	-1.2 (2.8)	-1.1	673	43.6 (3.8)	43.6	0 (2.7)	0	-1.2
Hemoglobin (g/dL) CN unit											
Baseline	1487	14.2 (1.3)	14.3	0 (0)	0	742	14.1 (1.3)	14	0 (0)	0	0
Week 4	1433	13.9 (1.3)	14	-0.3 (0.6)	-0.3	726	14 (1.2)	14.1	-0.1 (0.6)	-0.1	-0.2
Week 8	1398	13.8 (1.3)	13.9	-0.4 (0.7)	-0.4	718	14 (1.2)	14.1	0 (0.7)	0	-0.4
Week 12	1424	13.8 (1.3)	13.9	-0.4 (0.7)	-0.4	718	14.1 (1.2)	14.1	0 (0.7)	0	-0.4
Week 24	1396	13.8 (1.3)	13.9	-0.4 (0.8)	-0.4	707	14 (1.3)	14.1	-0.1 (0.7)	-0.1	-0.3
Week 36	1370	13.6 (1.3)	13.7	-0.6 (0.8)	-0.6	685	13.8 (1.3)	13.9	-0.3 (0.8)	-0.3	-0.3
Week 52	1344	13.6 (1.3)	13.7	-0.6 (0.9)	-0.6	673	13.9 (1.3)	13.9	-0.2 (0.9)	-0.2	-0.4
Hemoglobin A1C (%) CN unit											
Baseline	1487	6.1 (0.8)	5.9	0 (0)	0	742	6 (0.8)	5.8	0 (0)	0	0
Week 4	25	5.8 (0.4)	5.8	0 (0.2)	0	23	5.7 (0.4)	5.7	-0.1 (0.2)	0	0.1
Week 8	19	5.9 (0.7)	5.8	-0.1 (0.2)	-0.1	7	5.8 (0.7)	5.6	0 (0.3)	0.1	-0.1
Week 12	1418	6 (0.8)	5.8	-0.1 (0.3)	-0.1	720	6.1 (0.9)	5.8	0 (0.4)	0	-0.1
Week 24	36	5.9 (0.7)	5.8	0 (0.5)	0	22	5.8 (0.7)	5.7	-0.1 (0.2)	-0.1	0.1
Week 36	20	6.1 (0.9)	5.9	0 (0.4)	-0.1	13	7.2 (2.3)	6.4	0.6 (1.4)	0	-0.6
Week 52	1357	6.1 (0.8)	5.9	0 (0.4)	0	684	6.1 (1)	5.9	0.1 (0.6)	0	-0.1
Leukocytes (10^9/L) CN unit											
Baseline	1487	6.6 (1.8)	6.3	0 (0)	0	742	6.5 (1.7)	6.2	0 (0)	0	0
Week 4	1433	6.5 (1.9)	6.2	-0.1 (1.4)	-0.1	726	6.6 (1.7)	6.4	0.2 (1.3)	0.1	-0.3
Week 8	1398	6.5 (1.9)	6.2	-0.1 (1.3)	-0.1	718	6.6 (1.7)	6.5	0.2 (1.4)	0.2	-0.3
Week 12	1424	6.4 (1.9)	6	-0.2 (1.4)	-0.2	718	6.5 (1.8)	6.3	0.1 (1.3)	0	-0.3
Week 24	1396	6.3 (1.8)	6	-0.2 (1.3)	-0.2	707	6.6 (1.8)	6.4	0.1 (1.4)	0.1	-0.3
Week 36	1370	6.5 (1.9)	6.2	0 (1.3)	-0.1	685	6.7 (1.9)	6.5	0.3 (1.5)	0.1	-0.3
Week 52	1344	6.4 (1.9)	6.1	-0.2 (1.4)	-0.2	673	6.6 (2)	6.3	0.1 (1.5)	0.1	-0.3

Laboratory Parameters	Bempedoic Acid (N=1487) n (%)					Placebo (N=742) n (%)					Difference of Mean CFB
Week	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	
Lymphocytes (10^9/L) CN unit											
Baseline	1487	1.8 (0.7)	1.7	0 (0)	0	742	1.8 (0.6)	1.7	0 (0)	0	0
Week 4	1433	1.9 (0.7)	1.8	0.1 (0.3)	0.1	726	1.9 (0.7)	1.8	0.1 (0.4)	0.1	0
Week 8	1397	1.9 (0.7)	1.8	0.1 (0.3)	0	718	1.9 (0.7)	1.8	0.1 (0.4)	0.1	0
Week 12	1424	1.8 (0.7)	1.7	0 (0.4)	0	718	1.8 (0.6)	1.7	0 (0.3)	0	0
Week 24	1396	1.8 (0.6)	1.7	0 (0.4)	0	707	1.8 (0.6)	1.7	0 (0.4)	0	0
Week 36	1370	1.8 (0.7)	1.8	0 (0.4)	0	685	1.9 (0.7)	1.8	0.1 (0.4)	0.1	-0.1
Week 52	1344	1.8 (0.7)	1.7	0 (0.4)	0	673	1.8 (0.7)	1.7	0 (0.4)	0	0
Monocytes (10^9/L) CN unit											
Baseline	1487	0.4 (0.1)	0.4	0 (0)	0	742	0.4 (0.1)	0.4	0 (0)	0	0
Week 4	1433	0.4 (0.2)	0.4	0 (0.1)	0	726	0.4 (0.1)	0.4	0 (0.1)	0	0
Week 8	1397	0.4 (0.1)	0.4	0 (0.1)	0	718	0.4 (0.1)	0.4	0 (0.1)	0	0
Week 12	1424	0.4 (0.1)	0.4	0 (0.1)	0	718	0.4 (0.1)	0.4	0 (0.1)	0	0
Week 24	1396	0.4 (0.1)	0.4	0 (0.1)	0	707	0.4 (0.2)	0.4	0 (0.1)	0	0
Week 36	1370	0.5 (0.2)	0.4	0 (0.1)	0	685	0.5 (0.2)	0.4	0 (0.1)	0	0
Week 52	1344	0.4 (0.1)	0.4	0 (0.1)	0	673	0.4 (0.2)	0.4	0 (0.1)	0	0
Neutrophils (10^9/L) CN unit											
Baseline	1487	4.1 (1.4)	3.8	0 (0)	0	742	4 (1.4)	3.8	0 (0)	0	0
Week 4	1433	3.9 (1.5)	3.6	-0.2 (1.3)	-0.2	726	4.1 (1.4)	3.9	0.1 (1.2)	0.1	-0.3
Week 8	1397	3.9 (1.4)	3.6	-0.2 (1.2)	-0.2	718	4 (1.4)	3.9	0 (1.2)	0	-0.2
Week 12	1424	3.9 (1.5)	3.6	-0.2 (1.2)	-0.2	718	4 (1.5)	3.8	0 (1.2)	0	-0.2
Week 24	1396	3.9 (1.5)	3.6	-0.2 (1.2)	-0.2	707	4.1 (1.5)	3.8	0.1 (1.2)	0	-0.3
Week 36	1370	4 (1.5)	3.7	-0.1 (1.2)	-0.1	685	4.2 (1.6)	3.9	0.2 (1.4)	0	-0.3
Week 52	1344	3.9 (1.5)	3.7	-0.1 (1.2)	-0.1	673	4.1 (1.6)	3.9	0.1 (1.3)	0	-0.2
Platelets (10^9/L) CN unit											
Baseline	1484	232.8 (63.3)	226	0 (0)	0	741	231.4 (60)	224	0 (0)	0	0
Week 4	1421	251.4 (67.7)	241	19.5 (37.5)	17	724	233.6 (60.5)	226	2.4 (30.8)	2	17.1
Week 8	1389	253.5 (71.8)	244	21.3 (38.8)	19	716	235 (62.5)	226	3.5 (34.5)	3	17.8
Week 12	1421	253.9 (77.9)	243	21.7 (42.2)	19	717	233.3 (61.7)	226	2.4 (33.6)	2	19.3
Week 24	1390	249.6 (72.7)	239	17.9 (41.4)	15	706	234.9 (63.5)	224	3.4 (36.4)	2	14.5
Week 36	1367	252.1 (70.9)	243	20.3 (40.8)	17	685	236.4 (65.5)	225.5	4.8 (40.3)	3	15.5
Week 52	1340	254.7 (69.8)	246.5	23 (42.2)	20	670	238.4 (63.2)	228	7.5 (36.2)	6	15.5

Laboratory Parameters	Bempedoic Acid (N=1487) n (%)					Placebo (N=742) n (%)					Difference of Mean CFB
Week	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	N	Mean (SD)	Median	Mean (SD) CFB	Median CFB	
Prothrombin intl. normalized ratio (RATIO) CN unit											
Baseline	1487	1.1 (0.4)	1	0 (0)	0	741	1.1 (0.4)	1	0 (0)	0	0
Week 4	26	1.4 (0.6)	1.1	-0.2 (0.7)	0	20	1.4 (0.7)	1	-0.1 (0.7)	0	-0.1
Week 8	7	1.5 (0.8)	1	0.3 (0.4)	0.1	3	1.1 (0.1)	1	0 (0)	0	0.3
Week 12	476	1.2 (0.4)	1.1	0 (0.3)	0	246	1.2 (0.5)	1	0 (0.3)	0	0
Week 24	16	1.4 (1.2)	1.1	0.2 (1.2)	0	8	1.7 (1.1)	1.1	0.3 (0.6)	0	-0.1
Week 52	41	1.3 (0.5)	1.1	0 (0.6)	0	12	1 (0.1)	1	0 (0.1)	-0.1	0
Prothrombin time (sec) CN unit											
Baseline	1487	14.4 (4.3)	13.5	0 (0)	0	741	14.5 (3.6)	13.6	0 (0)	0	0
Week 4	26	16.5 (5.6)	13.8	-5.4 (20.9)	0	20	16.6 (6)	13.7	-0.7 (5.8)	0	-4.7
Week 8	7	17.8 (7.5)	13.7	-13.2 (41.2)	0.5	3	13.9 (1.4)	13.2	-0.1 (0.4)	0	-13.1
Week 12	477	15 (3.8)	13.9	0.5 (2.7)	0.3	246	14.8 (4)	13.6	-0.2 (2.6)	0	0.7
Week 24	16	16.9 (9.3)	14	1.9 (9.3)	0.1	8	19.7 (9.1)	14.7	2.6 (4.6)	0.5	-0.7
Week 52	41	16 (4.7)	14.1	-0.1 (5.2)	0.3	12	13.4 (0.8)	13.6	-0.2 (0.6)	-0.2	0.1
Reticulocytes (10^9/L) CN unit											
Week 12	6	71 (17.8)	67	0 (0)	0	3	90 (12)	90	0 (0)	0	0
Week 24	2	57.5 (17.7)	57.5	0 (0)	0	2	74.5 (14.8)	74.5	0 (0)	0	0

Source: adlbchem.xpt, adlbhema.xpt, and adlburin.xpt; Software: Python
Abbreviations: CFB, change from baseline; CN, conventional units; N, number of subjects in group; SD, standard deviation

17.1.5. Adverse Events

Table 130. Recoded Adverse Events

Verbatim Term	Coded As (AEDECOD)	Recoded to (AEDECOD)
Acute on chronic kidney disease	Chronic kidney disease	Acute kidney injury
General weakness on effort	Exercise tolerance decreased	Asthenia
Syncopal episode related to complete heart block	Syncope	Atrioventricular block complete
Bacteria in urine	Bacterial test	Bacteriuria
Bacteria in urine	Bacterial test positive	Bacteriuria
Bacteria in urine	Bacterial test positive	Bacteriuria
Elevated bacteria in urine	Bacterial test positive	Bacteriuria
Positive bacteria in urinalysis	Bacterial test positive	Bacteriuria
Positive bacteria in urine	Bacterial test positive	Bacteriuria

Verbatim Term	Coded As (AEDECOD)	Recoded to (AEDECOD)
Positive bacteria in urine analysis	Bacterial test positive	Bacteriuria
Positive bacteria in urinalysis	Bacterial test positive	Bacteriuria
Presence of bacteria in urine	Bacterial test positive	Bacteriuria
Urinalysis bacteria	Bacterial test positive	Bacteriuria
Urinalysis positive for bacteria	Bacterial test positive	Bacteriuria
Thoracic chest pain due to known coronary one vessel disease	Coronary artery disease	Angina pectoris
Decreased eGFR	Human epidermal growth factor receptor decreased	Decreased glomerular filtration rate
Inflammation of diverticula of the large intestine	Colitis	Diverticulitis
Gastrointestinal related chest pain	Noncardiac chest pain	Dyspepsia
Indigestion type chest pain	Noncardiac chest pain	Dyspepsia
Food blocks in throat	Foreign body in respiratory tract	Dysphagia
Lower back pain due to fall	Back pain	Fall
Coccyx contusion due to a fall on the stairs	Bone contusion	Fall
Bruises due to fall	Contusion	Fall
Facial bruising secondary to fall	Contusion	Fall
Pain of the chest on left side after fall – musculoskeletal related	Post-traumatic pain	Fall
Left shoulder hematoma secondary to fall	Traumatic hematoma	Fall
Left femoral systolic murmur ii/vi	Cardiac murmur	Femoral bruit
Right femoral systolic murmur i-ii/vi	Cardiac murmur	Femoral bruit
Erosive gastropathy	Gastric disorder	Gastritis
Gastric gastropathy	Gastric disorder	Gastritis
Gastropathia antralis	Gastric disorder	Gastritis
Gastropathy erythemiatous-erosion	Gastric disorder	Gastritis
Headache with blurred vision	Vision blurred	Headache
Spontaneous fracture of first lumbar vertebra	Pathological fracture	Lumbar vertebral fracture
Myalgia due to IP	Adverse drug reaction	Myalgia
Muscular discomfort left leg	Limb discomfort	Myalgia
Intensification of buttocks pain	Musculoskeletal pain	Myalgia
Sore buttocks	Musculoskeletal pain	Myalgia
Bilateral muscle pain in legs	Pain in extremity	Myalgia
Calfs muscle pain	Pain in extremity	Myalgia
Bilateral lower leg tenderness	Pain in extremity	Myalgia
Bilateral thigh pain	Pain in extremity	Myalgia
Calf pain	Pain in extremity	Myalgia
Calfs pain	Pain in extremity	Myalgia
Aggravation of calfs pain	Pain in extremity	Myalgia
Thighs pain	Pain in extremity	Myalgia

Verbatim Term	Coded As (AEDECOD)	Recoded to (AEDECOD)
Right upper arm biceps aches	Pain in extremity	Myalgia
Periodic pain in the calf	Pain in extremity	Myalgia
Pain in the calf	Pain in extremity	Myalgia
Intermittent right calf pain	Pain in extremity	Myalgia
Intermittent aches bilateral posterior thighs	Pain in extremity	Myalgia
Intensification of thighs pain	Pain in extremity	Myalgia
Chronic pancreatitis exacerbation	Pancreatitis	Pancreatitis chronic
Weakness in the course of fever	Asthenia	Pyrexia
Damage of muscle attachment of left thoracic muscle	Muscle injury	Tendon rupture
Left should rotator cuff tear	Rotator cuff syndrome	Tendon rupture
Left tear of rotator cuff	Rotator cuff syndrome	Tendon rupture
Right rotator cuff tear	Rotator cuff syndrome	Tendon rupture
Right shoulder torn rotator cuff	Rotator cuff syndrome	Tendon rupture
Second degree burns of stomach	Burn of internal organs	Thermal burn
Accelerated angina	Angina pectoris	Unstable angina
Aggravation of stable angina	Angina pectoris	Unstable angina
Angina pectoris requiring hospitalization	Angina pectoris	Unstable angina
Deterioration of angina pectoris	Angina pectoris	Unstable angina
Deterioration of stable angina	Angina pectoris	Unstable angina
Exacerbation of exertional angina	Angina pectoris	Unstable angina
Exacerbation of stenocardia	Angina pectoris	Unstable angina
Increased frequency angina pectoris	Angina pectoris	Unstable angina
Increased frequency of angina attacks	Angina pectoris	Unstable angina
Increasing episodes of cardiac chest pain	Angina pectoris	Unstable angina
Worsening angina	Angina pectoris	Unstable angina
Worsening angina pain	Angina pectoris	Unstable angina
Worsening angina pectoris	Angina pectoris	Unstable angina
Worsening cardiac chest pain	Angina pectoris	Unstable angina
Worsening of angina on effort	Angina pectoris	Unstable angina
Worsening of angina pectoris	Angina pectoris	Unstable angina
Worsening of angina pectoris symptoms	Angina pectoris	Unstable angina
Worsening of stable angina	Angina pectoris	Unstable angina
Worsening of stable angina pectoris	Angina pectoris	Unstable angina
Worsening stable angina	Angina pectoris	Unstable angina
Increased difficulty passing urine	Dysuria	Urinary retention
Ventricular fibrillation and flutter	Ventricular arrhythmia	Ventricular fibrillation
Vomiting and abdo discomfort, ? food poisoning	Food poisoning	Vomiting

Source: ADAE
Abbreviations: AEDECOD, preferred term; eGFR, estimated glomerular filtration rate

17.1.5.1. Deaths

Table 131. Deaths in Safety Population, Trial 040

Arm Subject ID	Age/ Sex	Dosing Duration (Days)	Study Day of Death	Days since Drug Exposure	Cause of Death		Narrative	Rev.[1]
					MedDRA PT	Verbatim Term		
Bempedoic Acid								
(b) (6)	69 F	114	114	0	Cardiac failure	Heart failure	Sudden death (collapsed during dinner, +cpr, not resuscitated); autopsy: heart failure	Possible
	55 M	192	192	0	Ischemic cerebral infarction	Ischemic apoplex	Procedural complication: cerebral bleed s/p thrombectomy and lysis for l mca occlusion	Unlikely
	63 M	60	61	0	Myocardial infarction	Myocardial infarction		Possible
	75 M	330			Multiple organ dysfunction syndrome, sepsis	Multi organ failure, sepsis	Surgical complication: bile leak s/p laparoscopic cholecystectomy	Highly unlikely
	76 M	227	233	6	Cardiac failure	Cardiac decompensation	Pulmonary abscess resulting in cardiopulmonary failure	Unlikely
	75 M	235	252	17	Metastases to liver	Liver metastasis unknown primary resulting in death	Diagnosed day 240, symptoms present day 169	Possible
	68 M	30	48	30	Myocardial ischemia, hypertensive heart disease	Death due to ischemic heart disease, hypertensive heart disease	Sudden death (found unresponsive, +cpr, not resuscitated); autopsy: ischemic heart disease and hypertension	Possible
	64 M	1	28	27	Myocardial infarction	Myocardial infarction		Possible
	72 M	85	124	39	Lung neoplasm malignant	Lung cancer left	Diagnosed day 17, former smoker	Highly unlikely
	81 M	252	303	51	Lung neoplasm malignant	Lung cancer	Diagnosed day 142, former smoker	Unlikely

Arm Subject ID	Age/ Sex	Dosing Duration (Days)	Study Day of Death	Days since Drug Exposure	Cause of Death		Narrative	Rev.[1]
					MedDRA PT	Verbatim Term		
(b) (6)	67 F	148	204	56	Lung squamous cell carcinoma metastatic	Squamous cell carcinoma of lungs with metastases to central nervous system	Diagnosed day 139, former smoker	Unlikely
	69 M	306	386	80	Lung neoplasm	Death due to tumor or right lung	Diagnosed day 343, current smoker	Possible
	79 M	3	87	84	Lung adenocarcinoma	Lung adenocarcinoma	Diagnosed day 27, former smoker	Unlikely
	63 M	253	339	86	Myocardial infarction	Myocardial infarction		Possible
	73 M	161	255	94	Septic shock	Septic shock	Surgical complication: anastomotic dehiscence s/p sigmoid colectomy for sigmoid adenocarcinoma (diagnosed day 162)	Unlikely
	66 M	84	178	7	Myocardial infarction	Myocardial infarction		Possible
	64 M	30	239	209	Adenocarcinoma pancreas	Pancreatic adenocarcinoma	Diagnosed day 228, current smoker	Possible
Placebo								
(b) (6)	64 M	160	160	0	Death	Death due to unknown origin	Died at home, no autopsy; +cv adjudication	Possible
	66 M	170	174	4	Peritonitis, septic shock	Acute peritonitis, septic shock with multiple organ failure	Procedural complication: cecal perforation during colonoscopy for colon neoplasm	Highly unlikely
	88 M	23	73	50	Death	Death of unknown cause	No details provided, +cv adjudication	Possible
	64 M	68			Gastric ulcer perforation, peritonitis	Perforation of the stomach ulcer, acute peritonitis	H/o osteoarthritis and chronic NSAID use	Unlikely

Arm Subject ID	Age/ Sex	Dosing Duration (Days)	Study Day of Death	Days since Drug Exposure	Cause of Death MedDRA PT	Cause of Death Verbatim Term	Narrative	Rev.[1]
(b) (6)	58 M	84			Intestinal angina, peripheral embolism	Angina abdominal, embolia of left arm	Surgical complication: cardiopulmonary failure during surgery	Unlikely

Source: Reviewer's analysis [adae.xpt, adsl.xpt; Software: JMP]
[1] 5-point scale: highly l kely, likely, possible, unlikely, highly unlikely
Abbreviations: Invest., investigator's assessment; MedDRA, Medical Dictionary for Regulatory Activities; Rev., reviewer's assessment; PT, preferred term; NSAID, nonsteroidal anti-inflammatory drug

Table 132. List of Deaths in Safety Population, Trial 047

Arm Subject ID	Age/ Sex	Dosing Duration (Days)	Study Day of Death	Days since Drug Exposure	Cause of Death MedDRA PT	Cause of Death Verbatim Term	Narrative	Rev.[1]
Bempedoic Acid								
(b) (6)	64 M	147			Gas poisoning	Acute poisoning with carbon dioxide		Highly unlikely
	65 M	175	175	0	Arteriosclerosis coronary artery	Coronary artery atheroma with probable superimposed thrombosis	Sudden death (found dead in kitchen); autopsy consistent with myocardial infarction	Possible
	78 F	9	9	0	Myocardial infarction	Myocardial infarction		Possible
	46 M	264	264	0	Death	Unknown cause of death	Sudden death (per wife), no autopsy	Possible
	79 F	214	217	3	Cardiac arrest	Cardiac arrest	Acute myocardial infarction (stemi)	Possible
	66 F	29			Septic shock	Septic shock with multiple organ failure	Procedural complication: small bowel perforation during ercp	Highly unlikely
	65 M	276	345	69	Renal failure, cardiac failure	Renal failure, heart failure hospitalization	Renal failure requiring dialysis s/p nephrectomy for renal cell cancer (diagnosed day 215)	Unlikely

Arm Subject ID	Age/ Sex	Dosing Duration (Days)	Study Day of Death	Days since Drug Exposure	Cause of Death		Narrative	Rev.[1]
					MedDRA PT	Verbatim Term		
(b) (6)	76 F	50			Varicose vein ruptured	Exsanguination due to varicose vein rupture of the lower leg		Highly unlikely
Placebo								
(b) (6)	64 M	170	170	0	Acute coronary syndrome	Acute coronary syndrome	Out-of-hospital cardiac arrest; coronary angiogram negative for acute obstruction, ecg no acute arrythmia	Possible
	74 M	290	291	1	Coronary artery disease	Sudden death (worsening coronary artery disease)	Sudden death (collapsed, +cpr, not resuscitated); no autopsy	Possible
	72 F	18	54	36	Cardiopulmonary failure	Circulatory-respiratory failure	"severe cardiopulmonary failure event", no additional details provided	Possible

Source: Reviewer's analysis [adae.xpt, adsl.xpt; Software: JMP]
[1] 5-point scale: highly l kely, likely, possible, unlikely, highly unlikely
Abbreviations: Invest., investigator's assessment; MedDRA, Medical Dictionary for Regulatory Activities; Rev., reviewer's assessment; PT, preferred term; s/p, status/post

17.1.5.2. Custom MedDRA Queries

Table 133. Grouped Queries of Treatment-Emergent Adverse Events by Descending Difference Order, Safety Population, Trials 040 and 047

	Trial 040		Trial 047		Pooled Safety Population	
Grouped Term	Bempedoic Acid (N=1487) n (%)	Placebo (N=742) n (%)	Bempedoic Acid (N=522) n (%)	Placebo (N=257) n (%)	Bempedoic Acid (N=2009) n (%)	Placebo (N=999) n (%)
Increased uric acid	34 (2.3)	5 (0.7)	36 (6.9)	6 (2.3)	70 (3.5)	11 (1.1)
Renal impairment	68 (4.6)	18 (2.4)	22 (4.2)	8 (3.1)	90 (4.5)	26 (2.6)
Elevated transaminases	35 (2.4)	8 (1.1)	14 (2.7)	4 (1.6)	49 (2.4)	12 (1.2)
Anemia	57 (3.8)	21 (2.8)	15 (2.9)	4 (1.6)	72 (3.6)	25 (2.5)
Benign prostatic hyperplasia	27 (1.8)	6 (0.8)	8 (1.5)	0 (0.0)	35 (1.7)	6 (0.6)
Gout	19 (1.3)	3 (0.4)	12 (2.3)	2 (0.8)	31 (1.5)	5 (0.5)
Abdominal pain/discomfort	60 (4.0)	22 (3.0)	13 (2.5)	5 (1.9)	73 (3.6)	27 (2.7)
Skin infection	24 (1.6)	4 (0.5)	5 (1.0)	2 (0.8)	29 (1.4)	6 (0.6)
Tendon disorder	12 (0.8)	2 (0.3)	6 (1.1)	0 (0.0)	18 (0.9)	2 (0.2)
Diarrhea	82 (5.5)	34 (4.6)	17 (3.3)	9 (3.5)	99 (4.9)	43 (4.3)
Atrial arrhythmias	25 (1.7)	11 (1.5)	11 (2.1)	2 (0.8)	36 (1.8)	13 (1.3)
Myopathy	135 (9.1)	61 (8.2)	21 (4.0)	12 (4.7)	156 (7.8)	73 (7.3)
Thyroid nodules	7 (0.5)	1 (0.1)	7 (1.3)	1 (0.4)	14 (0.7)	2 (0.2)
Gi irritation	38 (2.6)	13 (1.8)	7 (1.3)	5 (1.9)	45 (2.2)	18 (1.8)
Dysphagia	9 (0.6)	1 (0.1)	2 (0.4)	0 (0.0)	11 (0.5)	1 (0.1)
Lung tumors	6 (0.4)	0 (0.0)	4 (0.8)	1 (0.4)	10 (0.5)	1 (0.1)
Cartilage disorder	6 (0.4)	1 (0.1)	3 (0.6)	0 (0.0)	9 (0.4)	1 (0.1)
Pruritus	18 (1.2)	7 (0.9)	5 (1.0)	1 (0.4)	23 (1.1)	8 (0.8)
Wound infection	8 (0.5)	2 (0.3)	2 (0.4)	0 (0.0)	10 (0.5)	2 (0.2)
Genitourinary infection--men only	102 (6.9)	61 (8.2)	38 (7.3)	7 (2.7)	140 (7.0)	68 (6.8)
Stroke	15 (1.0)	5 (0.7)	4 (0.8)	2 (0.8)	19 (0.9)	7 (0.7)
Exfoliative skin condition	16 (1.1)	6 (0.8)	2 (0.4)	1 (0.4)	18 (0.9)	7 (0.7)
Poor wound healing	2 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)	5 (0.2)	0 (0.0)
Supraventricular arrhythmias	4 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)	6 (0.3)	1 (0.1)
Urine crystals	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Tooth loss/decay	11 (0.7)	6 (0.8)	4 (0.8)	0 (0.0)	15 (0.7)	6 (0.6)
Cholecystitis	5 (0.3)	1 (0.1)	2 (0.4)	1 (0.4)	7 (0.3)	2 (0.2)
Urinary tract infection	94 (6.3)	57 (7.7)	33 (6.3)	5 (1.9)	127 (6.3)	62 (6.2)
Small bone fractures	7 (0.5)	2 (0.3)	2 (0.4)	2 (0.8)	9 (0.4)	4 (0.4)
Renal stones	14 (0.9)	7 (0.9)	7 (1.3)	3 (1.2)	21 (1.0)	10 (1.0)
Bradycardia	12 (0.8)	6 (0.8)	3 (0.6)	1 (0.4)	15 (0.7)	7 (0.7)
Vertebral body fractures	1 (0.1)	0 (0.0)	2 (0.4)	1 (0.4)	3 (0.1)	1 (0.1)

	Trial 040		Trial 047		Pooled Safety Population	
Grouped Term	Bempedoic Acid (N=1487) n (%)	Placebo (N=742) n (%)	Bempedoic Acid (N=522) n (%)	Placebo (N=257) n (%)	Bempedoic Acid (N=2009) n (%)	Placebo (N=999) n (%)
Carotid artery disease	9 (0.6)	6 (0.8)	5 (1.0)	1 (0.4)	14 (0.7)	7 (0.7)
Fractures—overall	22 (1.5)	6 (0.8)	4 (0.8)	7 (2.7)	26 (1.3)	13 (1.3)
Truncal fractures	7 (0.5)	2 (0.3)	0 (0.0)	1 (0.4)	7 (0.3)	3 (0.3)
Ligament disorder	2 (0.1)	3 (0.4)	4 (0.8)	0 (0.0)	6 (0.3)	3 (0.3)
Genitourinary infection	84 (5.6)	53 (7.1)	34 (6.5)	7 (2.7)	118 (5.9)	60 (6.0)
Osteomalacia	3 (0.2)	3 (0.4)	5 (1.0)	2 (0.8)	8 (0.4)	5 (0.5)
Cardiopulmonary failure	2 (0.1)	1 (0.1)	2 (0.4)	2 (0.8)	4 (0.2)	3 (0.3)
Bone pain	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.0)	1 (0.1)
Volume overload	1 (0.1)	1 (0.1)	2 (0.4)	1 (0.4)	3 (0.1)	2 (0.2)
Acute heart failure	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.4)	2 (0.1)	2 (0.2)
Tachycardia	7 (0.5)	1 (0.1)	0 (0.0)	3 (1.2)	7 (0.3)	4 (0.4)
Aortic atherosclerotic disease	6 (0.4)	5 (0.7)	2 (0.4)	1 (0.4)	8 (0.4)	6 (0.6)
Long bone fractures	7 (0.5)	2 (0.3)	0 (0.0)	3 (1.2)	7 (0.3)	5 (0.5)
Av block	1 (0.1)	3 (0.4)	1 (0.2)	1 (0.4)	2 (0.1)	4 (0.4)
Coronary artery disease	20 (1.3)	11 (1.5)	16 (3.1)	10 (3.9)	36 (1.8)	21 (2.1)
Angina	36 (2.4)	27 (3.6)	17 (3.3)	3 (1.2)	53 (2.6)	30 (3.0)
Myocardial infarction	19 (1.3)	11 (1.5)	6 (1.1)	5 (1.9)	25 (1.2)	16 (1.6)
Peripheral artery disease	18 (1.2)	12 (1.6)	6 (1.1)	5 (1.9)	24 (1.2)	17 (1.7)
Hypertension	62 (4.2)	37 (5.0)	17 (3.3)	8 (3.1)	79 (3.9)	45 (4.5)
Joint pain	128 (8.6)	80 (10.8)	36 (6.9)	13 (5.1)	164 (8.2)	93 (9.3)
Acute coronary syndrome	45 (3.0)	25 (3.4)	16 (3.1)	17 (6.6)	61 (3.0)	42 (4.2)
Edema	32 (2.2)	26 (3.5)	6 (1.1)	5 (1.9)	38 (1.9)	31 (3.1)
Heart failure	61 (4.1)	42 (5.7)	19 (3.6)	11 (4.3)	80 (4.0)	53 (5.3)

Source: adae.xpt; Software: Python
Abbreviations: N, number of subjects in group; n, number of subjects with given adverse event

Table 134. Grouped Queries and Preferred Terms of Treatment-Emergent Adverse Events by Descending Difference Order, Safety Population, Trials 040 and 047

	Trial 040		Trial 047		Pooled Safety Population	
Grouped Term Preferred Term	Bempedoic Acid (N=1487) n (%)	Placebo (N=742) n (%)	Bempedoic Acid (N=522) n (%)	Placebo (N=257) n (%)	Bempedoic Acid (N=2009) n (%)	Placebo (N=999) n (%)
Increased uric acid	34 (2.3)	5 (0.7)	36 (6.9)	6 (2.3)	70 (3.5)	11 (1.1)
Blood uric acid increased	19 (1.3)	3 (0.4)	14 (2.7)	1 (0.4)	33 (1.6)	4 (0.4)
Hyperuricaemia	15 (1.0)	2 (0.3)	22 (4.2)	5 (1.9)	37 (1.8)	7 (0.7)
Renal impairment	68 (4.6)	18 (2.4)	22 (4.2)	8 (3.1)	90 (4.5)	26 (2.6)
Renal failure	14 (0.9)	1 (0.1)	2 (0.4)	0 (0.0)	16 (0.8)	1 (0.1)
Glomerular filtration rate decreased	8 (0.5)	0 (0.0)	4 (0.8)	1 (0.4)	12 (0.6)	1 (0.1)
Blood creatinine increased	12 (0.8)	3 (0.4)	4 (0.8)	1 (0.4)	16 (0.8)	4 (0.4)
Blood urine present	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)	0 (0.0)
Proteinuria	5 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)	7 (0.3)	1 (0.1)
Renal impairment	6 (0.4)	1 (0.1)	5 (1.0)	3 (1.2)	11 (0.5)	4 (0.4)
Acute kidney injury	5 (0.3)	2 (0.3)	2 (0.4)	1 (0.4)	7 (0.3)	3 (0.3)
Blood urea increased	1 (0.1)	1 (0.1)	2 (0.4)	0 (0.0)	3 (0.1)	1 (0.1)
Nephropathy	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.4)	2 (0.1)	1 (0.1)
Protein urine present	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)	1 (0.1)
Red blood cells urine positive	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Haematuria	16 (1.1)	8 (1.1)	3 (0.6)	2 (0.8)	19 (0.9)	10 (1.0)
Elevated transaminases	35 (2.4)	8 (1.1)	14 (2.7)	4 (1.6)	49 (2.4)	12 (1.2)
Aspartate aminotransferase increased	22 (1.5)	3 (0.4)	4 (0.8)	0 (0.0)	26 (1.3)	3 (0.3)
Alanine aminotransferase increased	13 (0.9)	2 (0.3)	6 (1.1)	0 (0.0)	19 (0.9)	2 (0.2)
Hepatic enzyme increased	7 (0.5)	0 (0.0)	1 (0.2)	2 (0.8)	8 (0.4)	2 (0.2)
Hepatic enzyme abnormal	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Hepatic function abnormal	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Liver function test increased	3 (0.2)	1 (0.1)	2 (0.4)	1 (0.4)	5 (0.2)	2 (0.2)
Transaminases increased	0 (0.0)	1 (0.1)	4 (0.8)	1 (0.4)	4 (0.2)	2 (0.2)
Liver function test abnormal	2 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.2)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Anemia	57 (3.8)	21 (2.8)	15 (2.9)	4 (1.6)	72 (3.6)	25 (2.5)
Anaemia	43 (2.9)	16 (2.2)	14 (2.7)	3 (1.2)	57 (2.8)	19 (1.9)
Haemoglobin decreased	7 (0.5)	3 (0.4)	1 (0.2)	0 (0.0)	8 (0.4)	3 (0.3)
Red blood cell count decreased	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Normocytic anaemia	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Mean cell volume increased	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Anaemia macrocytic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Haematocrit decreased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Microcytic anaemia	2 (0.1)	2 (0.3)	0 (0.0)	1 (0.4)	2 (0.1)	3 (0.3)
Benign prostatic hyperplasia	27 (1.8)	6 (0.8)	8 (1.5)	0 (0.0)	35 (1.7)	6 (0.6)
Benign prostatic hyperplasia	13 (0.9)	3 (0.4)	5 (1.0)	0 (0.0)	18 (0.9)	3 (0.3)
Urinary retention	9 (0.6)	2 (0.3)	2 (0.4)	0 (0.0)	11 (0.5)	2 (0.2)
Prostatic specific antigen increased	3 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	4 (0.2)	0 (0.0)
Prostatomegaly	2 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.1)	0 (0.0)
Prostatism	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Urine flow decreased	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Gout	19 (1.3)	3 (0.4)	12 (2.3)	2 (0.8)	31 (1.5)	5 (0.5)
Gout	18 (1.2)	2 (0.3)	11 (2.1)	2 (0.8)	29 (1.4)	4 (0.4)
Gouty arthritis	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Metatarsalgia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Abdominal pain/discomfort	60 (4.0)	22 (3.0)	13 (2.5)	5 (1.9)	73 (3.6)	27 (2.7)
Abdominal pain	18 (1.2)	7 (0.9)	8 (1.5)	1 (0.4)	26 (1.3)	8 (0.8)
Abdominal discomfort	8 (0.5)	1 (0.1)	1 (0.2)	0 (0.0)	9 (0.4)	1 (0.1)
Abdominal pain lower	5 (0.3)	1 (0.1)	1 (0.2)	0 (0.0)	6 (0.3)	1 (0.1)
Gastric disorder	4 (0.3)	1 (0.1)	1 (0.2)	0 (0.0)	5 (0.2)	1 (0.1)
Abdominal pain upper	23 (1.5)	8 (1.1)	2 (0.4)	4 (1.6)	25 (1.2)	12 (1.2)
Abdominal distension	6 (0.4)	4 (0.5)	0 (0.0)	0 (0.0)	6 (0.3)	4 (0.4)
Skin infection	24 (1.6)	4 (0.5)	5 (1.0)	2 (0.8)	29 (1.4)	6 (0.6)
Cellulitis	12 (0.8)	3 (0.4)	5 (1.0)	1 (0.4)	17 (0.8)	4 (0.4)
Erysipelas	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)	0 (0.0)
Skin infection	4 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.2)	1 (0.1)
Skin exfoliation	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Periorbital cellulitis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Excoriation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Tendon disorder	12 (0.8)	2 (0.3)	6 (1.1)	0 (0.0)	18 (0.9)	2 (0.2)
Tendon rupture	6 (0.4)	0 (0.0)	4 (0.8)	0 (0.0)	10 (0.5)	0 (0.0)
Tendon disorder	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Tendonitis	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)	1 (0.1)
Tendon pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Enthesopathy	1 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)	2 (0.1)	1 (0.1)
Tendon injury	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Diarrhea	82 (5.5)	34 (4.6)	17 (3.3)	9 (3.5)	99 (4.9)	43 (4.3)
Gastroenteritis	19 (1.3)	4 (0.5)	1 (0.2)	2 (0.8)	20 (1.0)	6 (0.6)
Frequent bowel movements	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Diarrhoea	61 (4.1)	30 (4.0)	16 (3.1)	7 (2.7)	77 (3.8)	37 (3.7)
Faecal volume increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Diarrhoea haemorrhagic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Atrial arrhythmias	25 (1.7)	11 (1.5)	11 (2.1)	2 (0.8)	36 (1.8)	13 (1.3)
Atrial fibrillation	23 (1.5)	9 (1.2)	11 (2.1)	2 (0.8)	34 (1.7)	11 (1.1)
Atrial tachycardia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Atrial flutter	2 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.2)
Myopathy	135 (9.1)	61 (8.2)	21 (4.0)	12 (4.7)	156 (7.8)	73 (7.3)
Blood creatine phosphokinase increased	35 (2.4)	13 (1.8)	4 (0.8)	3 (1.2)	39 (1.9)	16 (1.6)
Myositis	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	0 (0.0)
Musculoskeletal discomfort	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)	1 (0.1)
Myalgia	91 (6.1)	45 (6.1)	16 (3.1)	8 (3.1)	107 (5.3)	53 (5.3)
Red blood cells urine positive	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Muscular weakness	9 (0.6)	4 (0.5)	2 (0.4)	1 (0.4)	11 (0.5)	5 (0.5)
Muscle fatigue	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Muscle tightness	1 (0.1)	3 (0.4)	0 (0.0)	0 (0.0)	1 (0.0)	3 (0.3)
Thyroid nodules	7 (0.5)	1 (0.1)	7 (1.3)	1 (0.4)	14 (0.7)	2 (0.2)
Thyroid mass	3 (0.2)	0 (0.0)	3 (0.6)	0 (0.0)	6 (0.3)	0 (0.0)
Benign neoplasm of thyroid gland	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Goitre	3 (0.2)	1 (0.1)	4 (0.8)	1 (0.4)	7 (0.3)	2 (0.2)
GI irritation	38 (2.6)	13 (1.8)	7 (1.3)	5 (1.9)	45 (2.2)	18 (1.8)
Gastritis	16 (1.1)	6 (0.8)	4 (0.8)	1 (0.4)	20 (1.0)	7 (0.7)
Dyspepsia	22 (1.5)	7 (0.9)	3 (0.6)	3 (1.2)	25 (1.2)	10 (1.0)
Duodenitis	2 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.1)	0 (0.0)
Oesophagitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Dysphagia	9 (0.6)	1 (0.1)	2 (0.4)	0 (0.0)	11 (0.5)	1 (0.1)
Dysphagia	9 (0.6)	1 (0.1)	1 (0.2)	0 (0.0)	10 (0.5)	1 (0.1)
Oesophageal obstruction	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Lung tumors	6 (0.4)	0 (0.0)	4 (0.8)	1 (0.4)	10 (0.5)	1 (0.1)
Pulmonary mass	1 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)	4 (0.2)	0 (0.0)
Lung neoplasm malignant	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	0 (0.0)
Lung adenocarcinoma	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Neuroendocrine tumour of the lung	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Lung squamous cell carcinoma metastatic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Non–small cell lung cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Cartilage disorder	6 (0.4)	1 (0.1)	3 (0.6)	0 (0.0)	9 (0.4)	1 (0.1)
Meniscus injury	6 (0.4)	1 (0.1)	3 (0.6)	0 (0.0)	9 (0.4)	1 (0.1)
Chondromalacia	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Pruritus	18 (1.2)	7 (0.9)	5 (1.0)	1 (0.4)	23 (1.1)	8 (0.8)
Pruritus	15 (1.0)	5 (0.7)	4 (0.8)	1 (0.4)	19 (0.9)	6 (0.6)
Pruritus generalized	3 (0.2)	2 (0.3)	1 (0.2)	0 (0.0)	4 (0.2)	2 (0.2)
Wound infection	8 (0.5)	2 (0.3)	2 (0.4)	0 (0.0)	10 (0.5)	2 (0.2)
Postoperative wound infection	2 (0.1)	0 (0.0)	2 (0.4)	0 (0.0)	4 (0.2)	0 (0.0)
Wound infection	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Incision site inflammation	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Inflammation of wound	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Medical device site joint infection	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Post procedural inflammation	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Implant site infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Infected skin ulcer	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Genitourinary infection--men only	102 (6.9)	61 (8.2)	38 (7.3)	7 (2.7)	140 (7.0)	68 (6.8)
Bacteriuria	11 (0.7)	3 (0.4)	1 (0.2)	0 (0.0)	12 (0.6)	3 (0.3)
Leukocyturia	1 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)	4 (0.2)	0 (0.0)
Prostatitis	4 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)	6 (0.3)	1 (0.1)
Pyelonephritis chronic	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.1)	0 (0.0)
Urine analysis abnormal	7 (0.5)	2 (0.3)	0 (0.0)	0 (0.0)	7 (0.3)	2 (0.2)
Pyelonephritis	3 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)	3 (0.1)	1 (0.1)
White blood cells urine	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Urinary tract infection viral	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Nitrite urine present	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Urethritis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Dysuria	2 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.2)
Urine abnormality	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.2)
White blood cells urine positive	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Cystitis	7 (0.5)	6 (0.8)	2 (0.4)	1 (0.4)	9 (0.4)	7 (0.7)
Urinary tract infection	71 (4.8)	47 (6.3)	26 (5.0)	5 (1.9)	97 (4.8)	52 (5.2)
Stroke	15 (1.0)	5 (0.7)	4 (0.8)	2 (0.8)	19 (0.9)	7 (0.7)
Ischaemic stroke	2 (0.1)	0 (0.0)	4 (0.8)	2 (0.8)	6 (0.3)	2 (0.2)
Aphasia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Cerebral infarction	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Dysarthria	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Ischaemic cerebral infarction	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Speech disorder	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Transient ischaemic attack	5 (0.3)	2 (0.3)	0 (0.0)	0 (0.0)	5 (0.2)	2 (0.2)
Cerebrovascular accident	3 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	3 (0.1)	2 (0.2)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Exfoliative skin condition	16 (1.1)	6 (0.8)	2 (0.4)	1 (0.4)	18 (0.9)	7 (0.7)
Erysipelas	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)	0 (0.0)
Blister	4 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.2)	1 (0.1)
Oral pain	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Skin exfoliation	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Dermatitis exfoliative	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Pain of skin	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Sunburn	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Tongue ulceration	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Excoriation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Drug eruption	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Mouth ulceration	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Drug hypersensitivity	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.0)	1 (0.1)
Skin ulcer	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Mucosal inflammation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Poor wound healing	2 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)	5 (0.2)	0 (0.0)
Blood albumin decreased	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Protein total decreased	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Postoperative thoracic procedure complication	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Abdominal wound dehiscence	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Supraventricular arrhythmias	4 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)	6 (0.3)	1 (0.1)
Arrhythmia supraventricular	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.1)	0 (0.0)
Supraventricular tachycardia	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Supraventricular extrasystoles	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Urine crystals	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Crystalluria	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Crystal urine present	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Tooth loss/decay	11 (0.7)	6 (0.8)	4 (0.8)	0 (0.0)	15 (0.7)	6 (0.6)
Dental caries	4 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.2)	1 (0.1)
Loose tooth	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Toothache	6 (0.4)	4 (0.5)	3 (0.6)	0 (0.0)	9 (0.4)	4 (0.4)
Tooth fracture	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Cholecystitis	5 (0.3)	1 (0.1)	2 (0.4)	1 (0.4)	7 (0.3)	2 (0.2)
Cholecystitis	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	0 (0.0)
Cholecystitis acute	1 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)	2 (0.1)	1 (0.1)
Cholecystitis chronic	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	1 (0.0)	1 (0.1)
Urinary tract infection	94 (6.3)	57 (7.7)	33 (6.3)	5 (1.9)	127 (6.3)	62 (6.2)
Bacteriuria	11 (0.7)	3 (0.4)	1 (0.2)	0 (0.0)	12 (0.6)	3 (0.3)
Leukocyturia	1 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)	4 (0.2)	0 (0.0)
Polyuria	1 (0.1)	0 (0.0)	2 (0.4)	0 (0.0)	3 (0.1)	0 (0.0)
Nitrite urine present	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Pollakiuria	10 (0.7)	6 (0.8)	3 (0.6)	0 (0.0)	13 (0.6)	6 (0.6)
Urinary tract infection viral	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
White blood cells urine	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Dysuria	2 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.2)
Urine abnormality	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.2)
White blood cells urine positive	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Urinary tract infection	71 (4.8)	47 (6.3)	26 (5.0)	5 (1.9)	97 (4.8)	52 (5.2)
Small bone fractures	7 (0.5)	2 (0.3)	2 (0.4)	2 (0.8)	9 (0.4)	4 (0.4)
Facial bones fracture	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Wrist fracture	3 (0.2)	1 (0.1)	1 (0.2)	1 (0.4)	4 (0.2)	2 (0.2)
Foot fracture	2 (0.1)	0 (0.0)	1 (0.2)	1 (0.4)	3 (0.1)	1 (0.1)
Fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Ankle fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Renal stones	14 (0.9)	7 (0.9)	7 (1.3)	3 (1.2)	21 (1.0)	10 (1.0)
Nephrolithiasis	12 (0.8)	6 (0.8)	4 (0.8)	1 (0.4)	16 (0.8)	7 (0.7)
Calculus bladder	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Renal colic	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.4)	2 (0.1)	2 (0.2)
Calculus urinary	0 (0.0)	1 (0.1)	3 (0.6)	1 (0.4)	3 (0.1)	2 (0.2)
Bradycardia	12 (0.8)	6 (0.8)	3 (0.6)	1 (0.4)	15 (0.7)	7 (0.7)
Bradycardia	11 (0.7)	3 (0.4)	3 (0.6)	1 (0.4)	14 (0.7)	4 (0.4)
Sinus bradycardia	1 (0.1)	3 (0.4)	1 (0.2)	0 (0.0)	2 (0.1)	3 (0.3)
Vertebral body fractures	1 (0.1)	0 (0.0)	2 (0.4)	1 (0.4)	3 (0.1)	1 (0.1)
Fracture pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Thoracic vertebral fracture	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.4)	2 (0.1)	1 (0.1)
Transitional vertebrae	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Lumbar vertebral fracture	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	1 (0.0)	1 (0.1)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Carotid artery disease	9 (0.6)	6 (0.8)	5 (1.0)	1 (0.4)	14 (0.7)	7 (0.7)
Carotid artery disease	2 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.1)	0 (0.0)
Carotid artery stenosis	3 (0.2)	1 (0.1)	1 (0.2)	1 (0.4)	4 (0.2)	2 (0.2)
Cerebral hypoperfusion	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Cerebrosclerosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Carotid arteriosclerosis	2 (0.1)	3 (0.4)	2 (0.4)	1 (0.4)	4 (0.2)	4 (0.4)
Carotid bruit	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.2)
Fractures—overall	22 (1.5)	6 (0.8)	4 (0.8)	7 (2.7)	26 (1.3)	13 (1.3)
Facial bones fracture	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Scapula fracture	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Femur fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Upper limb fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Clavicle fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Fibula fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Foot fracture	2 (0.1)	0 (0.0)	1 (0.2)	1 (0.4)	3 (0.1)	1 (0.1)
Fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Fracture pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Humerus fracture	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Radius fracture	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.1)	1 (0.1)
Sternal fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Thoracic vertebral fracture	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.4)	2 (0.1)	1 (0.1)
Transitional vertebrae	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Wrist fracture	3 (0.2)	1 (0.1)	1 (0.2)	1 (0.4)	4 (0.2)	2 (0.2)
Hip fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Femoral neck fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Ankle fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Lower limb fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Lumbar vertebral fracture	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	1 (0.0)	1 (0.1)
Rib fracture	3 (0.2)	2 (0.3)	0 (0.0)	1 (0.4)	3 (0.1)	3 (0.3)
Truncal fractures	7 (0.5)	2 (0.3)	0 (0.0)	1 (0.4)	7 (0.3)	3 (0.3)
Scapula fracture	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Clavicle fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Sternal fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Rib fracture	3 (0.2)	2 (0.3)	0 (0.0)	1 (0.4)	3 (0.1)	3 (0.3)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Ligament disorder	2 (0.1)	3 (0.4)	4 (0.8)	0 (0.0)	6 (0.3)	3 (0.3)
Ligament sprain	2 (0.1)	2 (0.3)	3 (0.6)	0 (0.0)	5 (0.2)	2 (0.2)
Joint dislocation	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Ligament rupture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Genitourinary infection	84 (5.6)	53 (7.1)	34 (6.5)	7 (2.7)	118 (5.9)	60 (6.0)
Prostatitis	4 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)	6 (0.3)	1 (0.1)
Pyelonephritis chronic	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.1)	0 (0.0)
Pyelonephritis	3 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)	3 (0.1)	1 (0.1)
Urethritis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Cystitis	7 (0.5)	6 (0.8)	2 (0.4)	1 (0.4)	9 (0.4)	7 (0.7)
Urinary tract infection	71 (4.8)	47 (6.3)	26 (5.0)	5 (1.9)	97 (4.8)	52 (5.2)
Osteomalacia	3 (0.2)	3 (0.4)	5 (1.0)	2 (0.8)	8 (0.4)	5 (0.5)
Osteopenia	2 (0.1)	2 (0.3)	2 (0.4)	0 (0.0)	4 (0.2)	2 (0.2)
Osteochondrosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Osteoporosis	1 (0.1)	1 (0.1)	2 (0.4)	2 (0.8)	3 (0.1)	3 (0.3)
Cardiopulmonary failure	2 (0.1)	1 (0.1)	2 (0.4)	2 (0.8)	4 (0.2)	3 (0.3)
Circulatory collapse	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Cardiac arrest	1 (0.1)	1 (0.1)	2 (0.4)	2 (0.8)	3 (0.1)	3 (0.3)
Bone pain	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.0)	1 (0.1)
Periostitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Bone pain	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Volume overload	1 (0.1)	1 (0.1)	2 (0.4)	1 (0.4)	3 (0.1)	2 (0.2)
Left atrial enlargement	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	2 (0.1)	1 (0.1)
Left ventricular dilatation	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Left ventricular enlargement	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Right atrial enlargement	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Left ventricular end-diastolic pressure increased	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Acute heart failure	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.4)	2 (0.1)	2 (0.2)
Acute pulmonary oedema	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Cardiac failure acute	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Acute left ventricular failure	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.0)	1 (0.1)
Tachycardia	7 (0.5)	1 (0.1)	0 (0.0)	3 (1.2)	7 (0.3)	4 (0.4)
Heart rate increased	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)	1 (0.1)
Tachycardia	4 (0.3)	0 (0.0)	0 (0.0)	3 (1.2)	4 (0.2)	3 (0.3)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Aortic atherosclerotic disease	6 (0.4)	5 (0.7)	2 (0.4)	1 (0.4)	8 (0.4)	6 (0.6)
Aortic dilatation	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Aortic bruit	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Aortic arteriosclerosis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Aortic aneurysm	4 (0.3)	3 (0.4)	2 (0.4)	1 (0.4)	6 (0.3)	4 (0.4)
Long bone fractures	7 (0.5)	2 (0.3)	0 (0.0)	3 (1.2)	7 (0.3)	5 (0.5)
Radius fracture	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.1)	1 (0.1)
Upper limb fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Fibula fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Humerus fracture	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Femur fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Lower limb fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Femoral neck fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Hip fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
AV block	1 (0.1)	3 (0.4)	1 (0.2)	1 (0.4)	2 (0.1)	4 (0.4)
Atrioventricular block second degree	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.4)	2 (0.1)	1 (0.1)
Atrioventricular block complete	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Atrioventricular block first degree	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Coronary artery disease	20 (1.3)	11 (1.5)	16 (3.1)	10 (3.9)	36 (1.8)	21 (2.1)
Arteriosclerosis coronary artery	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Coronary artery stenosis	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.1)	0 (0.0)
Coronary artery restenosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Coronary vascular graft occlusion	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Coronary artery occlusion	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.0)	1 (0.1)
Coronary artery disease	15 (1.0)	7 (0.9)	7 (1.3)	6 (2.3)	22 (1.1)	13 (1.3)
Myocardial ischaemia	4 (0.3)	3 (0.4)	5 (1.0)	4 (1.6)	9 (0.4)	7 (0.7)
Angina	36 (2.4)	27 (3.6)	17 (3.3)	3 (1.2)	53 (2.6)	30 (3.0)
Chest pain	10 (0.7)	4 (0.5)	3 (0.6)	1 (0.4)	13 (0.6)	5 (0.5)
Chest discomfort	6 (0.4)	5 (0.7)	1 (0.2)	0 (0.0)	7 (0.3)	5 (0.5)
Angina pectoris	20 (1.3)	18 (2.4)	13 (2.5)	2 (0.8)	33 (1.6)	20 (2.0)
Myocardial infarction	19 (1.3)	11 (1.5)	6 (1.1)	5 (1.9)	25 (1.2)	16 (1.6)
Electrocardiogram q wave abnormal	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Myocardial infarction	8 (0.5)	6 (0.8)	4 (0.8)	2 (0.8)	12 (0.6)	8 (0.8)
Acute myocardial infarction	11 (0.7)	5 (0.7)	2 (0.4)	3 (1.2)	13 (0.6)	8 (0.8)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Peripheral artery disease	18 (1.2)	12 (1.6)	6 (1.1)	5 (1.9)	24 (1.2)	17 (1.7)
Peripheral ischaemia	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Peripheral vascular disorder	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Femoral artery aneurysm	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Vascular stent restenosis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Peripheral artery aneurysm	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Poor peripheral circulation	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Peripheral artery stenosis	2 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)	3 (0.1)	1 (0.1)
Iliac artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Arteriosclerosis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vascular stent occlusion	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	1 (0.0)	1 (0.1)
Peripheral artery occlusion	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Femoral bruit	2 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.2)
Intermittent claudication	0 (0.0)	3 (0.4)	1 (0.2)	0 (0.0)	1 (0.0)	3 (0.3)
Peripheral arterial occlusive disease	8 (0.5)	6 (0.8)	3 (0.6)	5 (1.9)	11 (0.5)	11 (1.1)
Hypertension	62 (4.2)	37 (5.0)	17 (3.3)	8 (3.1)	79 (3.9)	45 (4.5)
Blood pressure increased	17 (1.1)	8 (1.1)	6 (1.1)	1 (0.4)	23 (1.1)	9 (0.9)
Blood pressure systolic increased	1 (0.1)	0 (0.0)	2 (0.4)	0 (0.0)	3 (0.1)	0 (0.0)
Blood pressure inadequately controlled	1 (0.1)	1 (0.1)	3 (0.6)	0 (0.0)	4 (0.2)	1 (0.1)
Hypertensive crisis	1 (0.1)	2 (0.3)	2 (0.4)	0 (0.0)	3 (0.1)	2 (0.2)
Orthostatic hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Hypertension	43 (2.9)	26 (3.5)	7 (1.3)	6 (2.3)	50 (2.5)	32 (3.2)
Joint pain	128 (8.6)	80 (10.8)	36 (6.9)	13 (5.1)	164 (8.2)	93 (9.3)
Arthritis	4 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.2)	1 (0.1)
Musculoskeletal pain	39 (2.6)	19 (2.6)	2 (0.4)	1 (0.4)	41 (2.0)	20 (2.0)
Metatarsalgia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Osteoarthritis	30 (2.0)	26 (3.5)	16 (3.1)	5 (1.9)	46 (2.3)	31 (3.1)
Arthralgia	65 (4.4)	44 (5.9)	18 (3.4)	8 (3.1)	83 (4.1)	52 (5.2)

Grouped Term Preferred Term	Trial 040 Bempedoic Acid (N=1487) n (%)	Trial 040 Placebo (N=742) n (%)	Trial 047 Bempedoic Acid (N=522) n (%)	Trial 047 Placebo (N=257) n (%)	Pooled Safety Population Bempedoic Acid (N=2009) n (%)	Pooled Safety Population Placebo (N=999) n (%)
Acute coronary syndrome	45 (3.0)	25 (3.4)	16 (3.1)	17 (6.6)	61 (3.0)	42 (4.2)
Hyperhidrosis	12 (0.8)	3 (0.4)	1 (0.2)	3 (1.2)	13 (0.6)	6 (0.6)
Cold sweat	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Electrocardiogram t wave inversion	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Acute myocardial infarction	11 (0.7)	5 (0.7)	2 (0.4)	3 (1.2)	13 (0.6)	8 (0.8)
Myocardial ischaemia	4 (0.3)	3 (0.4)	5 (1.0)	4 (1.6)	9 (0.4)	7 (0.7)
Acute coronary syndrome	1 (0.1)	2 (0.3)	0 (0.0)	1 (0.4)	1 (0.0)	3 (0.3)
Angina unstable	18 (1.2)	12 (1.6)	9 (1.7)	6 (2.3)	27 (1.3)	18 (1.8)
Edema	32 (2.2)	26 (3.5)	6 (1.1)	5 (1.9)	38 (1.9)	31 (3.1)
Oedema	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Swelling face	0 (0.0)	2 (0.3)	1 (0.2)	0 (0.0)	1 (0.0)	2 (0.2)
Oedema peripheral	17 (1.1)	11 (1.5)	4 (0.8)	2 (0.8)	21 (1.0)	13 (1.3)
Peripheral swelling	8 (0.5)	9 (1.2)	1 (0.2)	1 (0.4)	9 (0.4)	10 (1.0)
Weight increased	7 (0.5)	5 (0.7)	0 (0.0)	4 (1.6)	7 (0.3)	9 (0.9)
Heart failure	61 (4.1)	42 (5.7)	19 (3.6)	11 (4.3)	80 (4.0)	53 (5.3)
Cardiac failure chronic	1 (0.1)	0 (0.0)	5 (1.0)	1 (0.4)	6 (0.3)	1 (0.1)
Exercise tolerance decreased	2 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.1)	0 (0.0)
Dyspnoea exertional	5 (0.3)	0 (0.0)	1 (0.2)	2 (0.8)	6 (0.3)	2 (0.2)
Cardiac failure congestive	5 (0.3)	2 (0.3)	2 (0.4)	1 (0.4)	7 (0.3)	3 (0.3)
Acute pulmonary oedema	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Left ventricular failure	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.0)	1 (0.1)
Oedema	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Ejection fraction decreased	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.0)	1 (0.1)
Cardiac failure acute	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Acute left ventricular failure	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.0)	1 (0.1)
Oedema peripheral	17 (1.1)	11 (1.5)	4 (0.8)	2 (0.8)	21 (1.0)	13 (1.3)
Cardiac failure	6 (0.4)	5 (0.7)	1 (0.2)	2 (0.8)	7 (0.3)	7 (0.7)
Peripheral swelling	8 (0.5)	9 (1.2)	1 (0.2)	1 (0.4)	9 (0.4)	10 (1.0)
Dyspnoea	21 (1.4)	16 (2.2)	7 (1.3)	5 (1.9)	28 (1.4)	21 (2.1)

Source: adae.xpt; Software: Python
Abbreviations: AV, atrioventricular; GI, gastrointestinal; N, number of subjects in group; n, number of subjects with given adverse event

Table 135. Grouped Queries of Treatment-Emergent Adverse Events by Descending Difference Order, Safety Population, Trial 046

Grouped Term	Bempedoic Acid (N=234) n (%)	Placebo (N=111) n (%)
Hypertension	12 (5.1)	2 (1.8)
GI irritation	6 (2.6)	0 (0.0)
Acute coronary syndrome	6 (2.6)	0 (0.0)
Increased uric acid	6 (2.6)	0 (0.0)
Angina	8 (3.4)	1 (0.9)
Pruritus	4 (1.7)	0 (0.0)
Elevated transaminases	4 (1.7)	0 (0.0)
Anemia	3 (1.3)	0 (0.0)
Coronary artery disease	3 (1.3)	0 (0.0)
Joint pain	15 (6.4)	6 (5.4)
Exfoliative skin condition	2 (0.9)	0 (0.0)
Stroke	2 (0.9)	0 (0.0)
Gout	4 (1.7)	1 (0.9)
Myopathy	20 (8.5)	9 (8.1)
Wound infection	1 (0.4)	0 (0.0)
Long bone fractures	1 (0.4)	0 (0.0)
Myocardial infarction	1 (0.4)	0 (0.0)
Bone pain	1 (0.4)	0 (0.0)
Skin infection	1 (0.4)	0 (0.0)
Diarrhea	5 (2.1)	2 (1.8)
Heart failure	9 (3.8)	4 (3.6)
Fractures—overall	2 (0.9)	1 (0.9)
Peripheral artery disease	2 (0.9)	1 (0.9)
Edema	6 (2.6)	3 (2.7)
Renal impairment	4 (1.7)	2 (1.8)
Tendon disorder	1 (0.4)	1 (0.9)
Osteomalacia	1 (0.4)	1 (0.9)
Small bone fractures	1 (0.4)	1 (0.9)
Abdominal pain/discomfort	5 (2.1)	3 (2.7)
Aortic atherosclerotic disease	0 (0.0)	1 (0.9)
Bradycardia	0 (0.0)	1 (0.9)
Lung tumors	0 (0.0)	2 (1.8)
Renal stones	0 (0.0)	2 (1.8)
Urinary tract infection	10 (4.3)	9 (8.1)
Genitourinary infection--men only	14 (6.0)	11 (9.9)
Genitourinary infection	12 (5.1)	11 (9.9)

Source: adae.xpt; Software: Python
Abbreviations: GI, gastrointestinal; N, number of subjects in group; n, number of subjects with given adverse event

Table 136. Grouped Queries and Preferred Terms of Treatment-Emergent Adverse Events by Descending Difference Order, Safety Population, Trial 046

Grouped Term Preferred Term	Bempedoic Acid (N=234) n (%)	Placebo (N=111) n (%)
Hypertension	12 (5.1)	2 (1.8)
Hypertension	10 (4.3)	2 (1.8)
Blood pressure increased	2 (0.9)	0 (0.0)
GI irritation	6 (2.6)	0 (0.0)
Dyspepsia	5 (2.1)	0 (0.0)
Gastritis	2 (0.9)	0 (0.0)
Acute coronary syndrome	6 (2.6)	0 (0.0)
Angina unstable	4 (1.7)	0 (0.0)
Hyperhidrosis	2 (0.9)	0 (0.0)
Increased uric acid	6 (2.6)	0 (0.0)
Blood uric acid increased	4 (1.7)	0 (0.0)
Hyperuricaemia	2 (0.9)	0 (0.0)
Angina	8 (3.4)	1 (0.9)
Chest pain	3 (1.3)	0 (0.0)
Angina pectoris	2 (0.9)	0 (0.0)
Chest discomfort	3 (1.3)	1 (0.9)
Pruritus	4 (1.7)	0 (0.0)
Pruritus generalized	3 (1.3)	0 (0.0)
Pruritus	1 (0.4)	0 (0.0)
Elevated transaminases	4 (1.7)	0 (0.0)
Alanine aminotransferase increased	1 (0.4)	0 (0.0)
Hepatic enzyme increased	1 (0.4)	0 (0.0)
Hepatic function abnormal	1 (0.4)	0 (0.0)
Liver function test increased	1 (0.4)	0 (0.0)
Aspartate aminotransferase increased	1 (0.4)	0 (0.0)
Anemia	3 (1.3)	0 (0.0)
Anaemia	3 (1.3)	0 (0.0)
Coronary artery disease	3 (1.3)	0 (0.0)
Coronary artery disease	3 (1.3)	0 (0.0)
Joint pain	15 (6.4)	6 (5.4)
Arthralgia	14 (6.0)	5 (4.5)
Musculoskeletal pain	3 (1.3)	0 (0.0)
Osteoarthritis	1 (0.4)	3 (2.7)
Exfoliative skin condition	2 (0.9)	0 (0.0)
Mouth ulceration	1 (0.4)	0 (0.0)
Pain of skin	1 (0.4)	0 (0.0)
Stroke	2 (0.9)	0 (0.0)
Ischaemic stroke	1 (0.4)	0 (0.0)
Cerebrovascular accident	1 (0.4)	0 (0.0)
Aphasia	1 (0.4)	0 (0.0)
Gout	4 (1.7)	1 (0.9)
Gout	4 (1.7)	1 (0.9)
Myopathy	20 (8.5)	9 (8.1)
Blood creatine phosphokinase increased	5 (2.1)	0 (0.0)
Muscle tightness	1 (0.4)	0 (0.0)
Tenderness	1 (0.4)	0 (0.0)
Muscular weakness	1 (0.4)	2 (1.8)
Myalgia	13 (5.6)	8 (7.2)
Wound infection	1 (0.4)	0 (0.0)
Post procedural infection	1 (0.4)	0 (0.0)

Grouped Term Preferred Term	Bempedoic Acid (N=234) n (%)	Placebo (N=111) n (%)
Long bone fractures	1 (0.4)	0 (0.0)
Upper limb fracture	1 (0.4)	0 (0.0)
Myocardial infarction	1 (0.4)	0 (0.0)
Myocardial infarction	1 (0.4)	0 (0.0)
Bone pain	1 (0.4)	0 (0.0)
Bone pain	1 (0.4)	0 (0.0)
Skin infection	1 (0.4)	0 (0.0)
Cellulitis	1 (0.4)	0 (0.0)
Diarrhea	5 (2.1)	2 (1.8)
Gastroenteritis	1 (0.4)	0 (0.0)
Frequent bowel movements	1 (0.4)	0 (0.0)
Diarrhoea	3 (1.3)	2 (1.8)
Heart failure	9 (3.8)	4 (3.6)
Dyspnoea exertional	2 (0.9)	0 (0.0)
Oedema	1 (0.4)	0 (0.0)
Oedema peripheral	4 (1.7)	2 (1.8)
Dyspnoea	2 (0.9)	2 (1.8)
Fractures—overall	2 (0.9)	1 (0.9)
Upper limb fracture	1 (0.4)	0 (0.0)
Wrist fracture	1 (0.4)	0 (0.0)
Foot fracture	0 (0.0)	1 (0.9)
Peripheral artery disease	2 (0.9)	1 (0.9)
Femoral bruit	1 (0.4)	0 (0.0)
Peripheral arterial occlusive disease	1 (0.4)	0 (0.0)
Vascular calcification	0 (0.0)	1 (0.9)
Edema	6 (2.6)	3 (2.7)
Oedema	1 (0.4)	0 (0.0)
Oedema peripheral	4 (1.7)	2 (1.8)
Weight increased	1 (0.4)	1 (0.9)
Renal impairment	4 (1.7)	2 (1.8)
Renal failure	2 (0.9)	0 (0.0)
Renal impairment	1 (0.4)	0 (0.0)
Blood urine present	1 (0.4)	0 (0.0)
Acute kidney injury	0 (0.0)	1 (0.9)
Haematuria	0 (0.0)	1 (0.9)
Tendon disorder	1 (0.4)	1 (0.9)
Enthesopathy	1 (0.4)	0 (0.0)
Tendonitis	0 (0.0)	1 (0.9)
Osteomalacia	1 (0.4)	1 (0.9)
Osteoporosis	1 (0.4)	1 (0.9)
Small bone fractures	1 (0.4)	1 (0.9)
Wrist fracture	1 (0.4)	0 (0.0)
Foot fracture	0 (0.0)	1 (0.9)
Abdominal pain/discomfort	5 (2.1)	3 (2.7)
Abdominal discomfort	1 (0.4)	0 (0.0)
Abdominal pain	2 (0.9)	1 (0.9)
Abdominal pain upper	2 (0.9)	1 (0.9)
Abdominal distension	0 (0.0)	1 (0.9)
Aortic atherosclerotic disease	0 (0.0)	1 (0.9)
Aortic aneurysm	0 (0.0)	1 (0.9)
Bradycardia	0 (0.0)	1 (0.9)
Heart rate decreased	0 (0.0)	1 (0.9)

Grouped Term Preferred Term	Bempedoic Acid (N=234) n (%)	Placebo (N=111) n (%)
Lung tumors	0 (0.0)	2 (1.8)
Pulmonary mass	0 (0.0)	2 (1.8)
Renal stones	0 (0.0)	2 (1.8)
Nephrolithiasis	0 (0.0)	2 (1.8)
Urinary tract infection	10 (4.3)	9 (8.1)
Urinary tract infection pseudomonal	1 (0.4)	0 (0.0)
Nitrite urine	1 (0.4)	0 (0.0)
Dysuria	0 (0.0)	1 (0.9)
Urinary tract infection	8 (3.4)	9 (8.1)
Genitourinary infection--men only	14 (6.0)	11 (9.9)
Cystitis	2 (0.9)	0 (0.0)
Cystitis escherichia	1 (0.4)	0 (0.0)
Kidney infection	1 (0.4)	0 (0.0)
Nitrite urine	1 (0.4)	0 (0.0)
Urinary tract infection pseudomonal	1 (0.4)	0 (0.0)
Prostatitis	0 (0.0)	1 (0.9)
Escherichia pyelonephritis	0 (0.0)	1 (0.9)
Dysuria	0 (0.0)	1 (0.9)
Urinary tract infection	8 (3.4)	9 (8.1)
Genitourinary infection	12 (5.1)	11 (9.9)
Cystitis	2 (0.9)	0 (0.0)
Cystitis escherichia	1 (0.4)	0 (0.0)
Kidney infection	1 (0.4)	0 (0.0)
Escherichia pyelonephritis	0 (0.0)	1 (0.9)
Prostatitis	0 (0.0)	1 (0.9)
Urinary tract infection	8 (3.4)	9 (8.1)

Source: adae.xpt; Software: Python
Abbreviations: GI, gastrointestinal; N, number of subjects in group; n, number of subjects with given adverse event

Table 137. Grouped Queries of Treatment-Emergent Adverse Events by Descending Difference Order, Safety Population, Trial 048

Grouped Term	Bempedoic Acid (N=181) n (%)	Placebo (N=87) n (%)
Elevated transaminases	13 (7.2)	0 (0.0)
Increased uric acid	15 (8.3)	2 (2.3)
Renal impairment	8 (4.4)	1 (1.1)
Abdominal pain/discomfort	4 (2.2)	0 (0.0)
Joint pain	6 (3.3)	1 (1.1)
Angina	2 (1.1)	0 (0.0)
Renal stones	2 (1.1)	0 (0.0)
Diarrhea	2 (1.1)	0 (0.0)
Osteomalacia	2 (1.1)	0 (0.0)
Anemia	1 (0.6)	0 (0.0)
Heart failure	1 (0.6)	0 (0.0)
Gi irritation	1 (0.6)	0 (0.0)
Exfoliative skin condition	1 (0.6)	0 (0.0)
Av block	1 (0.6)	0 (0.0)
Hypertension	3 (1.7)	1 (1.1)
Myopathy	7 (3.9)	3 (3.4)
Edema	1 (0.6)	1 (1.1)
Dysphagia	0 (0.0)	1 (1.1)
Stroke	0 (0.0)	1 (1.1)
Tendon disorder	0 (0.0)	1 (1.1)
Genitourinary infection--men only	8 (4.4)	5 (5.7)
Urinary tract infection	8 (4.4)	5 (5.7)
Genitourinary infection	5 (2.8)	5 (5.7)

Source: adae.xpt; Software: Python
Abbreviations: N, number of subjects in group; n, number of subjects with given adverse event

Table 138. Grouped Queries and Preferred Terms of Treatment-Emergent Adverse Events by Descending Difference Order, Safety Population, Trial 048

Grouped Term Preferred Term	Bempedoic Acid (N=181) n (%)	Placebo (N=87) n (%)
Elevated transaminases	13 (7.2)	0 (0.0)
Liver function test increased	7 (3.9)	0 (0.0)
Alanine aminotransferase increased	3 (1.7)	0 (0.0)
Aspartate aminotransferase increased	3 (1.7)	0 (0.0)
Liver function test abnormal	2 (1.1)	0 (0.0)
Hepatic enzyme increased	1 (0.6)	0 (0.0)
Increased uric acid	15 (8.3)	2 (2.3)
Blood uric acid increased	14 (7.7)	2 (2.3)
Hyperuricaemia	1 (0.6)	0 (0.0)
Renal impairment	8 (4.4)	1 (1.1)
Glomerular filtration rate decreased	4 (2.2)	0 (0.0)
Blood creatinine increased	3 (1.7)	0 (0.0)
Renal impairment	1 (0.6)	0 (0.0)
Red blood cells urine positive	1 (0.6)	0 (0.0)
Haematuria	1 (0.6)	0 (0.0)
Renal failure	2 (1.1)	1 (1.1)
Abdominal pain/discomfort	4 (2.2)	0 (0.0)
Abdominal pain	2 (1.1)	0 (0.0)
Abdominal distension	2 (1.1)	0 (0.0)
Joint pain	6 (3.3)	1 (1.1)
Arthralgia	3 (1.7)	0 (0.0)
Musculoskeletal pain	2 (1.1)	0 (0.0)
Osteoarthritis	1 (0.6)	1 (1.1)
Angina	2 (1.1)	0 (0.0)
Chest discomfort	2 (1.1)	0 (0.0)
Renal stones	2 (1.1)	0 (0.0)
Nephrolithiasis	2 (1.1)	0 (0.0)
Diarrhea	2 (1.1)	0 (0.0)
Diarrhoea	2 (1.1)	0 (0.0)
Osteomalacia	2 (1.1)	0 (0.0)
Osteoporosis	1 (0.6)	0 (0.0)
Osteopenia	1 (0.6)	0 (0.0)
Anemia	1 (0.6)	0 (0.0)
Haematocrit decreased	1 (0.6)	0 (0.0)
Haemoglobin decreased	1 (0.6)	0 (0.0)
Heart failure	1 (0.6)	0 (0.0)
Peripheral swelling	1 (0.6)	0 (0.0)
GI irritation	1 (0.6)	0 (0.0)
Dyspepsia	1 (0.6)	0 (0.0)
Exfoliative skin condition	1 (0.6)	0 (0.0)
Mouth ulceration	1 (0.6)	0 (0.0)
AV block	1 (0.6)	0 (0.0)
Atrioventricular block	1 (0.6)	0 (0.0)
Hypertension	3 (1.7)	1 (1.1)
Blood pressure increased	2 (1.1)	0 (0.0)
Hypertension	1 (0.6)	1 (1.1)

Grouped Term Preferred Term	Bempedoic Acid (N=181) n (%)	Placebo (N=87) n (%)
Myopathy	7 (3.9)	3 (3.4)
Blood creatine phosphokinase increased	3 (1.7)	0 (0.0)
Muscular weakness	1 (0.6)	0 (0.0)
Red blood cells urine positive	1 (0.6)	0 (0.0)
Myalgia	3 (1.7)	2 (2.3)
Muscle rupture	0 (0.0)	1 (1.1)
Edema	1 (0.6)	1 (1.1)
Peripheral swelling	1 (0.6)	0 (0.0)
Weight increased	0 (0.0)	1 (1.1)
Dysphagia	0 (0.0)	1 (1.1)
Dysphagia	0 (0.0)	1 (1.1)
Stroke	0 (0.0)	1 (1.1)
Dysarthria	0 (0.0)	1 (1.1)
Tendon disorder	0 (0.0)	1 (1.1)
Tendonitis	0 (0.0)	1 (1.1)
Genitourinary infection--men only	8 (4.4)	5 (5.7)
Bacteriuria	1 (0.6)	0 (0.0)
Dysuria	1 (0.6)	0 (0.0)
Pyuria	1 (0.6)	0 (0.0)
White blood cells urine positive	1 (0.6)	0 (0.0)
Urinary tract infection	5 (2.8)	5 (5.7)
Urinary tract infection	8 (4.4)	5 (5.7)
White blood cells urine positive	1 (0.6)	0 (0.0)
Pyuria	1 (0.6)	0 (0.0)
Dysuria	1 (0.6)	0 (0.0)
Bacteriuria	1 (0.6)	0 (0.0)
Urinary tract infection	5 (2.8)	5 (5.7)
Genitourinary infection	5 (2.8)	5 (5.7)
Urinary tract infection	5 (2.8)	5 (5.7)

Source: adae.xpt; Software: Python
Abbreviations: AV, atrioventricular; GI, gastrointestinal; N, number of subjects in group; n, number of subjects with given adverse event

17.1.5.3. Adverse Event Subgroup Analyses

Table 139. Adverse Events[1] by Age Group, Safety Population, High CV Risk Pool, Trials 040 and 047, 52 Weeks

Event	Bempedoic Acid		Placebo	
	<65 Years (N=871) n (%)	≥65 Years (N=1138) n (%)	<65 Years (N=385) n (%)	≥65 Years (N=614) n (%)
Any AE	630 (72.3)	930 (81.7)	281 (73.0)	494 (80.5)
Moderate or severe AEs (Grade 3–5)[2]	423 (48.6)	694 (61.0)	174 (45.2)	360 (58.6)
SAE	140 (16.1)	223 (19.6)	61 (15.8)	112 (18.2)
AE leading to discontinuation of study drug	72 (8.3)	152 (13.4)	32 (8.3)	44 (7.2)
AE leading to interruption of study drug	92 (10.6)	152 (13.4)	33 (8.6)	64 (10.4)

Source: Reviewer's analysis; software: JMP
[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug
[2] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; Severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up
Abbreviations: AE, adverse event; SAE, serious adverse event; CV, cardiovascular; N, number of subjects in group; n, number of subjects with at least one event

Table 140. Adverse Events[1] by Sex, Safety Population, High CV Risk Pool, Trials 040 and 047, 52 Weeks

Event	Bempedoic Acid		Placebo	
	Male (N=1427) n (%)	Female (N=582) n (%)	Male (N=697) n (%)	Female (N=302) n (%)
Any AE	1102 (77.2)	458 (78.8)	527 (75.6)	248 (82.1)
Moderate or severe AEs (Grade 3–5)[2]	781 (54.7)	336 (57.7)	354 (50.8)	180 (59.6)
SAE	253 (17.7)	110 (18.9)	114 (16.4)	59 (19.5)
AE leading to discontinuation of study drug	147 (10.3)	77 (13.2)	51 (7.3)	25 (8.3)
AE leading to interruption of study drug	173 (12.1)	71 (12.2)	68 (9.8)	29 (9.6)

Source: Reviewer's analysis; software: JMP
[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug
[2] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; Severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up
Abbreviations: AE, adverse event; SAE, serious adverse event; CV, cardiovascular; N, number of subjects in group; n, number of subjects with at least one event

Table 141. Adverse Events[1] by Race, Safety Population, High CV Risk Pool, Trials 040 and 047, 52 Weeks

Event	Bempedoic Acid		Placebo	
	White (N=1913) n (%)	Non-White (N=96) n (%)	White (N=960) n (%)	Non-White (N=39) n (%)
Any AE	1497 (78.3)	63 (65.6)	753 (78.4)	22 (56.4)
Moderate or severe AEs (Grade 3–5)[2]	1084 (56.7)	33 (34.4)	515 (53.6)	19 (48.7)
SAE	355 (18.6)	8 (8.3)	168 (17.5)	5 (12.8)
AE leading to discontinuation of study drug	221 (11.6)	3 (3.1)	74 (7.7)	2 (5.1)
AE leading to interruption of study drug	235 (12.3)	9 (9.4)	95 (9.9)	2 (5.1)

Source: Reviewer's analysis; software: JMP
[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug
[2] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; Severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up
Abbreviations: AE, adverse event; SAE, serious adverse event; CV, cardiovascular; N, number of subjects in group; n, number of subjects with at least one event

Table 142. Adverse Events[1] by Ethnicity, Safety Population, High CV Risk Pool, Trials 040 and 047, 52 Weeks

	Bempedoic Acid		Placebo	
Event	Hispanic N=67 n (%)	Non-Hispanic N=1942 n (%)	Hispanic N=30 n (%)	Non-Hispanic N=969 n (%)
Any AE	28 (41.8)	1532 (78.9)	12 (40.0)	763 (78.7)
Moderate or severe AEs (Grade 3–5)[2]	15 (22.4)	1102 (56.7)	5 (16.7)	529 (54.6)
SAE	8 (11.9)	355 (18.3)	2 (6.7)	171 (17.6)
AE leading to discontinuation of study drug	2 (3.0)	222 (11.4)	0 (0.0)	76 (7.8)
AE leading to interruption of study drug	3 (4.5)	241 (12.4)	1 (3.3)	96 (9.9)

Source: Reviewer's analysis; software: JMP
[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug
[2] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; Severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up
Abbreviations: AE, adverse event; SAE, serious adverse event; CV, cardiovascular; N, number of subjects in group; n, number of subjects with at least one event

Table 143. Adverse Events[1] by Country, Safety Population, High CV Risk Pool, Trials 040 and 047, 52 Weeks

Event	U.S. N=517 n (%)	Non-U.S. N=1492 n (%)	U.S. N=256 n (%)	Non-U.S. N=743 n (%)
Any AE	374 (72.3)	1186 (79.5)	179 (69.9)	596 (80.2)
Moderate or severe AEs (Grade 3–5)[2]	242 (46.8)	875 (58.6)	115 (44.9)	419 (56.4)
SAE	78 (15.1)	285 (19.1)	37 (14.5)	136 (18.3)
AE leading to discontinuation of study drug	46 (8.9)	178 (11.9)	22 (8.6)	54 (7.3)
AE leading to interruption of study drug	66 (12.8)	178 (11.9)	22 (8.6)	75 (10.1)

Source: Reviewer's analysis; software: JMP
[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug
[2] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; Severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up
Abbreviations: AE, adverse event; SAE, serious adverse event; CV, cardiovascular; N, number of subjects in group; n, number of subjects with at least one event

17.2. Supplemental Data for Open-Label Extension Trial, 1002-050

Table 144. Duration of Exposure, Safety Population, Trial 050

	Bempedoic Acid (N=1462) n (%)
Duration of treatment (weeks)	
Mean (SD)	27.2 (24.2)
Median (min, max)	18.6 (0.0, 79.9)
Patients treated, by duration, n (%)	
<12 weeks	39 (2.7)
≥12 weeks	25 (1.7)
≥24 weeks	26 (1.8)
≥48 weeks	7 (0.5)
≥72 weeks	15 (1.0)

Source: adsl.xpt; Software: Python
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

Table 145. Treatment-Emergent Adverse Events, Safety Population, Trial 050

Adverse Event	Bempedoic Acid (N=1462) n (%)
Any TEAE	934 (63.9)
Serious TEAEs (SAEs)	198 (13.5)
TEAE leading to discontinuation of study drug	60 (4.1)
TEAE leading to dose modification of study drug	129 (8.8)
TEAE leading to interruption of study drug	129 (8.8)
TEAE leading to reduction of study drug	0 (0.0)
TEAE leading to delay of study drug	0 (0.0)

Source: adae.xpt; Software: Python
Abbreviations: N, number of subjects in group; n, number of subjects with given event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 146. Serious Adverse Events Occurring ≥0.3% by Descending Difference Order, Safety Population, Trial 050

Adverse Event	Bempedoic Acid (N=1462) n (%)
Coronary artery disease	11 (0.8)
Angina pectoris	9 (0.6)
Angina unstable	7 (0.5)
Atrial fibrillation	7 (0.5)
Myocardial ischaemia	7 (0.5)
Acute myocardial infarction	6 (0.4)
Cataract	6 (0.4)
Osteoarthritis	6 (0.4)
Cardiac failure	4 (0.3)
Myocardial infarction	5 (0.3)
Cholelithiasis	5 (0.3)
Pneumonia	5 (0.3)
Sepsis	5 (0.3)
Not coded	4 (0.3)
Acute kidney injury	5 (0.3)
Peripheral arterial occlusive disease	4 (0.3)

Source: adae.xpt; Software: Python
Abbreviations: N, number of subjects in group; n, number of subjects with given adverse event

Table 147. Treatment-Emergent Adverse Events Leading to Discontinuation by Descending Difference Order, Safety Population, Trial 050

Adverse Event	Bempedoic Acid (N=1462) n (%)
Treatment discontinuation due to TEAEs	60 (4.1)
Myalgia	4 (0.3)
Dizziness	5 (0.3)
Headache	4 (0.3)
Aspartate aminotransferase increased	3 (0.2)
Alanine aminotransferase increased	3 (0.2)
Muscle spasms	3 (0.2)
Diarrhoea	3 (0.2)
Pain in extremity	3 (0.2)
Adenocarcinoma of colon	1 (0.1)
Metastatic gastric cancer	1 (0.1)
B-cell lymphoma	1 (0.1)
Leukopenia	1 (0.1)
Allodynia	1 (0.1)
Muscular weakness	2 (0.1)
Arthralgia	1 (0.1)
Decreased appetite	1 (0.1)
Pancreatic carcinoma	1 (0.1)
Cerebrovascular accident	1 (0.1)
Balance disorder	1 (0.1)
Blood triglycerides increased	1 (0.1)
Haemorrhage intracranial	1 (0.1)
Lethargy	2 (0.1)
Presyncope	1 (0.1)
Not coded	1 (0.1)

Adverse Event	Bempedoic Acid (N=1462) n (%)
Irritability	1 (0.1)
Nervousness	1 (0.1)
Incontinence	1 (0.1)
Cough	1 (0.1)
Dermatitis contact	1 (0.1)
Skin warm	1 (0.1)
Glomerular filtration rate increased	1 (0.1)
Blood creatine phosphokinase increased	1 (0.1)
Blood glucose increased	1 (0.1)
Asthenia	1 (0.1)
Anginal equivalent	1 (0.1)
Cardiac failure congestive	1 (0.1)
Coronary artery disease	2 (0.1)
Myocardial ischaemia	1 (0.1)
Palpitations	1 (0.1)
Abdominal pain	2 (0.1)
Anal incontinence	1 (0.1)
Gastrooesophageal reflux disease	1 (0.1)
Nausea	2 (0.1)
Pancreatitis	1 (0.1)
Vomiting	1 (0.1)
Brain death	1 (0.1)
Acute myocardial infarction	1 (0.1)
Fatigue	2 (0.1)
Gait disturbance	1 (0.1)
Malaise	1 (0.1)
Vascular stent thrombosis	1 (0.1)
Cellulitis	1 (0.1)
Intervertebral discitis	1 (0.1)
Lymph node tuberculosis	1 (0.1)
Pulmonary tuberculosis	1 (0.1)
Sepsis	1 (0.1)
Fall	1 (0.1)
Intestinal anastomosis complication	1 (0.1)
Flushing	1 (0.1)

Source: adae.xpt; Software: Python
Abbreviations: N, number of subjects in group; n, number of subjects with given adverse event; TEAE, treatment-emergent adverse event

Table 148. Treatment-Emergent Adverse Events Occurring ≥1% by Descending Difference Order, Safety Population, Trial 050

Adverse Event	Bempedoic Acid (N=1462) n (%)
Nasopharyngitis	68 (4.7)
Urinary tract infection	52 (3.6)
Arthralgia	41 (2.8)
Dizziness	39 (2.7)
Upper respiratory tract infection	34 (2.3)
Muscle spasms	32 (2.2)
Pain in extremity	32 (2.2)
Diarrhoea	31 (2.1)
Bronchitis	28 (1.9)
Anaemia	28 (1.9)
Back pain	26 (1.8)
Myalgia	27 (1.8)
Osteoarthritis	27 (1.8)
Angina pectoris	23 (1.6)
Lower respiratory tract infection	24 (1.6)
Musculoskeletal pain	23 (1.6)
Headache	22 (1.5)
Hypertension	22 (1.5)
Cough	21 (1.4)
Atrial fibrillation	20 (1.4)
Cataract	20 (1.4)
Dyspnoea	19 (1.3)
Gastrooesophageal reflux disease	19 (1.3)
Sinusitis	17 (1.2)
Gout	18 (1.2)
Influenza	18 (1.2)
Abdominal pain	14 (1.0)
Coronary artery disease	14 (1.0)
Pneumonia	14 (1.0)
Fatigue	15 (1.0)
Noncardiac chest pain	15 (1.0)
Oedema peripheral	14 (1.0)
Type 2 diabetes mellitus	14 (1.0)
Fall	14 (1.0)
Nausea	15 (1.0)

Source: adae.xpt; Software: Python
Abbreviations: N, number of subjects in group; n, number of subjects with given adverse event

18. Mechanism of Action / Drug Resistance: Additional Information and Assessment

N/A

19. Other Drug Development Considerations: Additional Information and Assessment

N/A

20. Data Integrity-Related Consults (OSI, Other Inspections)

Clinical Inspection Summary

Date	12/19/2019
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Anthony Orencia, M.D., Ph.D., Acting Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Laura Higginbotham, M.D., M.P.H., Clinical Reviewer John Sharretts, M.D., Clinical Team Leader Kati Johnson, Senior Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	211616
Applicant	Esperion Therapeutics, Inc.
Drug	Bempedoic acid
NME	Yes
Therapeutic Classification	Antihyperlipidemic agent
Proposed Indication	Treatment of primary hyperlipidemia
Consultation Request Date	4/17/2019
Summary Goal Date	12/21/2019
Action Goal Date	2/21/2020
PDUFA Date	2/21/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) covering three clinical trials consisted of five domestic and three foreign clinical sites representing ten study sites, in addition to the sponsor.

The inspection of two clinical investigators listed below and the sponsor revealed regulatory deficiencies which are unlikely to have a significant impact on overall results. The inspection of the remaining clinical investigators revealed no regulatory violations. Based on the inspections, the study data generated are considered acceptable and may be used in support of this NDA.

THE FOLLOWING 21 PAGES HAVE BEEN WITHHELD AS DUPLICATE PAGES. PLEASE SEE THE CLINICAL INSPECTION SUMMARY DOCUMENT IN THE OTHER REVIEWS SECTION OF THIS APPROVAL PACKAGE

1

21. Labeling Summary of Considerations and Key Additional Information

The following major labeling decisions were conveyed to the Applicant:

- (b) (4) the indicated population to patients on maximally tolerated statin with HeFH or established ASCVD
- Removal (b) (4)
- Addition of tendon rupture and hyperuricemia to Warnings and Precautions
- Addition of BPH and atrial fibrillation to Section 6 of labeling
- Addition of drug-drug interaction with pravastatin in Section 7 of labeling
- Removal (b) (4)

22. Postmarketing Requirements and Commitments

Postmarketing Requirements

(1) Conduct a pharmacokinetic/pharmacodynamic study evaluating bempedoic acid in patients with heterozygous familial hypercholesterolemia (HeFH) aged 10 years to less than 18 years. The Phase 2 study will be a randomized, open-label, 6-week, dose-finding study of bempedoic acid in 36 patients aged 10 years to less than 18 years with HeFH on stable background lipid-modifying therapy with LDL-C ≥130 mg/dL.

Draft Protocol Submission:	March 2020
Final Protocol Submission:	August 2020
Study Completion:	March 2022
Final Report Submission:	August 2022

(2) Conduct an efficacy and safety study evaluating bempedoic acid in patients with heterozygous familial hypercholesterolemia (HeFH) aged 10 years to less than 18 years. The Phase 3 study will be a randomized, double-blind, placebo controlled, parallel group, 6-month, multicenter efficacy and safety study in 200 patients (randomized 1:1 to bempedoic acid and placebo), followed by a 6-month open-label extension in at least 100 patients assigned to bempedoic acid in pediatric patients aged 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C ≥130 mg/dL.

Draft Protocol Submission:	August 2022
Final Protocol Submission:	March 2023
Study Completion:	February 2026
Final Report Submission:	August 2026

(3) Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Nexletol (bempedoic acid) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years. Results will be analyzed and reported descriptively. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.

Draft Protocol Submission:	September 2020
Final Protocol Submission:	May 2021
Interim Report Submissions:	April 2022
	April 2023
	April 2024
	April 2025
	April 2026
	April 2027
	April 2028
	April 2029
	April 2030
	April 2031
Study Completion:	May 2032
Final Report Submission:	January 2033

(4) Perform a lactation study (milk only) in lactating women who have received therapeutic doses of Nexletol (bempedoic acid) using a validated assay to assess concentrations of bempedoic acid in breast milk and the effects on the breastfed infant.

Draft Protocol Submission:	September 2020
Final Protocol Submission:	April 2021
Study Completion:	April 2024
Final Report Submission:	December 2024

(5) Complete the ongoing randomized, double-blind, placebo-controlled, parallel group, multi-center trial in approximately 14,000 patients (randomized 1:1 to bempedoic acid and placebo) designed to assess the effects of bempedoic acid on the occurrence of major cardiovascular events. The trial will include evaluation of the effects of bempedoic acid on occurrence of tendinopathy, tendon rupture, atrial fibrillation, and renal impairment as adverse events of special interest.

Draft Protocol Submission:	June 2020
Final Protocol Submission:	September 2020
Trial Completion:	March 2023
Final Report Submission:	February 2024

23. Financial Disclosure

Table 149. Covered Clinical Studies, Trials 040, 046, 047, and 048

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1493 (Principal and Sub Investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

24. References

None.

25. Review Team

Table 150. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Kati Johnson
Nonclinical Reviewer	Lydia Haile
Nonclinical Team Leader	Calvin (Lee) Elmore
Office of Clinical Pharmacology Reviewer(s)	Tao Liu
Office of Clinical Pharmacology Team Leader(s)	Lian Ma Suryanarayana Sista
Clinical Reviewer	Laura Higginbotham
Clinical Team Leader	John Sharretts
Statistical Reviewer	Anna Ketterman
Statistical Team Leader	Feng Li
Cross-Disciplinary Team Leader	John Sharretts
Division Director (OCP)	Chandrahas Sahajwalla
Division Director (OB)	Mark Rothmann
Office Director (or designated signatory authority)	Mary Thanh Hai

Table 151. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Leeza Rahimi/John Amartey/Parmesa Patel/Muthukumar Ramaswamy/Donna Christner/Christina Capacci-Daniel/Ying Zhang/Kamrun Nahar/Haritha Mandula/Danae Christoulou
Patient Labeling	Sharon Williams/LaShawn Griffiths
OPDP	Charuni Shah
OSI	Cynthia Kleppinger/Anthony Orencia, Kassa Ayalew
OSE/DMEPA	Valerie Vaughn/Sevan Kolejian/Deveonne Hamilton-Stokes
DPMH	Jane Liedka/Miriam Dinatale

OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

Table 152. Signatures of Reviewers

Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Approved[1]**
Pharmacology/Toxicology	Lydia Haile, PhD	OND/ODE2/DMEP	IA, 5.1, 7.1, 7.7, 8.4,13 ☒ Authored ☐ Approved
Primary Reviewer	**Signature:** Lydia A. Haile -S Digitally signed by Lydia A. Haile -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lydia A. Haile -S, 0.9.2342.19200300.100.1.1=2000470805 Date: 2020.02.20 10:54:03 -05'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Approved**
Pharmacology/Toxicology	C. Lee Elmore, PhD	OND/ODE2/DMEP	IA, ES, 5.1, 7.1, 7.7, 8.4,13 ☐ Authored ☒ Approved
Secondary Reviewer	**Signature:** Calvin L. Elmore -S Digitally signed by Calvin L. Elmore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000356615, cn=Calvin L. Elmore -S Date: 2020.02.20 14:15:48 -05'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Approved**
Pharmacology/Toxicology	Timothy McGovern, PhD	OND	IA, 5.1, 7.1, 7.7, 8.4,13 ☐ Authored ☒ Approved
Tertiary Reviewer	**Signature:** Signed on behalf of Timothy McGovern Calvin L. Elmore -S Digitally signed by Calvin L. Elmore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000356615, cn=Calvin L. Elmore -S Date: 2020.02.20 14:17:12 -05'00'		
Discipline and Title or Role	**Reviewer Name**	Office/Division	Sections Authored/ Approved
Clinical Pharmacology	**Tao Liu, PhD**	OTS/OCP/DIIP	IA, 5, 6.1, 8.1, 8.2, 14 ☒ Authored ☐ Approved
Primary Reviewer	**Signature:** Tao Liu -S Digitally signed by Tao Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tao Liu -S, 0.9.2342.19200300.100.1.1=2001206753 Date: 2020.02.20 10:42:25 -05'00'		
Discipline and Title or Role	**Reviewer Name**	Office/Division	Sections Authored/ Approved
Clinical Pharmacology	**Suryanarayana Sista, PhD**	OTS/OCP/DCEP	IA, 5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Secondary Reviewer	**Signature:** Suryanarayana M. Sista -S Digitally signed by Suryanarayana M. Sista -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001007118, cn=Suryanarayana M. Sista -S Date: 2020.02.20 10:47:54 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Approved[1]
Clinical Pharmacology/Pharmacometrics	**Lian Ma, PhD**	OTS/OCP/DPM	IA, 5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Secondary Reviewer	**Signature:** Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2020.02.20 12:22:37 -05'00'		
Discipline and Title or Role	**Reviewer Name**	Office/Division	Sections Authored/ Approved
Clinical Pharmacology	**Chandrahas Sahajwalla, PhD**	OTS/OCP/DIIP	IA, 5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Division Director	**Signature:** Chandrahas G. Sahajwalla -S Digitally signed by Chandrahas G. Sahajwalla -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300079192, cn=Chandrahas G. Sahajwalla -S Date: 2020.02.20 14:02:26 -05'00'		
Discipline and Title or Role	**Reviewer Name**	Office/Division	Sections Authored/ Approved
Statistical	**Anna Kettermann, Dipl. Math, MA**	OTS/OB/DB2	IA, 6.2.3,6.3, 16 ☒ Authored ☐ Approved
Primary Reviewer	**Signature:** Anna Kettermann -S Digitally signed by Anna Kettermann -S Date: 2020.02.20 13:28:58 -05'00'		
Discipline and Title or Role	**Reviewer Name**	Office/Division	Sections Authored/ Approved
Statistical	**Feng Li, PhD**	OTS/OB/DB2	IA, 6.2.3,6.3,16 ☐ Authored ☒ Approved
Secondary Reviewer	**Signature:** Feng Li -S Digitally signed by Feng Li S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Feng Li S 0 9 2342 19200300 100 1 1=2000332337 Date: 2020 02 20 12:17 49 05'00'		
Discipline and Title or Role	**Reviewer Name**	Office/Division	Sections Authored/ Approved
Statistical	**Mark Rothmann, PhD**	OTS/OB/DB2	IA, 6.2.3,6.3,16 ☐ Authored ☒ Approved
Supervisor	**Signature:** Mark D. Rothmann -S Digitally signed by Mark D. Rothmann -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144907, cn=Mark D. Rothmann -S Date: 2020.02.20 16:00:27 -05'00'		
Discipline and Title or Role	**Reviewer Name**	Office/Division	Sections Authored/ Acknowledged/ Approved[1]

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Approved[1]
Clinical	**Laura Higginbotham, MD, MPH**	OND/ODE2/DMEP	IA, ES, 2,3,4,6.2.1, 6.2.2, 6.3, 6.4, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 8.3, 17, 21, 22, 23 ☒ Authored ☐ Approved
Primary Reviewer	**Signature:** Laura B. Higginbotham -S	Digitally signed by Laura B. Higginbotham -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002617854, cn=Laura B. Higginbotham -S Date: 2020.02.20 10:25:08 -05'00'	

[1] Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary.

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/s/

KATI JOHNSON
02/21/2020 10:19:44 AM

JOHN M SHARRETTS
02/21/2020 11:17:21 AM
I co-authored the Executive Summary of this Integrated Review. I approved and concur with the findings in the Integrated Assessment and Appendices.

MARY T THANH HAI
02/21/2020 11:27:32 AM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA 211616/SN-0001 (IND106654)
Drug Name:	Bempedoic acid tablets 180 mg (ETC-1002)
Indication(s):	(b) (4)
Applicant:	Esperion Therapeutics, Inc. 3891 Ranchero Drive, Suite 150 I Ann Arbor, MI 48108, USA (b) (4)
Date(s):	Received 4/1/2019
Documents Reviewed:	Studies rr1002-500-035 (rats) rr1002-500-036 (mice) were submitted on 2/20/2019 (via NDA 211616/SN0001) and the electronic tumor.xpt files were submitted on 4/3/2019 (via NDA 211616/SN0006).
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Nonclinical Team:	Lydia Haile, Ph.D; Calvin Elmore, Ph.D
Project Manager:	Kati Johnson
Keywords:	Carcinogenicity, Dose response

Table of Contents

Reference ID: 4465565

1 Summary

This review evaluates statistically the data of the 2-year oral carcinogenicity studies in Wistar Hannover rats and in CD1 mice. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). From the statistical point of view, the review concludes that ETC-1002 statistically decreased the survivals in male and female mice and that ETC-1002 caused statistically significant increases in the incidence of hepatocellular carcinomas and adenomas, alone or in combination in liver in males in both species, of follicular cell adenoma or combined with carcinoma in thyroid gland in male rats, and of islet cell adenoma combined with carcinoma in pancreas in male rats. See Table 1 for tumor incidences and p-values of the tumor types mentioned above.

Table 1: Tumor Types with Statistically Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Control

Animal	Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	3 mg/kg/day Low (L) P - C vs. L	10 mg/kg/day Mid (M) P - C vs. M	30 mg/kg/day High (H) P - C vs. H
Male Rats	Liver	Adenoma, Hepatocellular	0/65 (57)	0/65 (59)	1/65 (61)	7/65 (58)
			0.0001 *	NC	0.5169	0.0069 **
		Hepatocellular_A+C	0/65 (57)	0/65 (59)	2/65 (61)	8/65 (58)
			0.0000 *	NC	0.2651	0.0032 **
	Pancreas	Islet Cell_A+C	1/65 (57)	4/65 (59)	1/65 (61)	9/65 (58)
			0.0025 *	0.1930	0.7688	0.0088 **
	Thyroid Gland	Adenoma, Follicular Cell	0/65 (57)	2/65 (59)	4/65 (61)	9/65 (58)
			0.0005 *	0.2565	0.0680	0.0015 **
		Follicular-Cell_A+C	0/65 (57)	5/65 (59)	5/65 (61)	12/65 (59)
			0.0004 *	0.0312	0.0340	0.0002 **
Animal	**Organ name**	**Tumor name**	**0 mg Vehicle (C) P - Trend**	**25 mg/kg/day Low (L) P - C vs. L**	**75 mg/kg/day Mid (M) P - C vs. M**	**150 mg/kg/day High (H) P - C vs. H**
Male Mice	Liver	Adenoma, Hepatocellular	12/72 (52)	16/77 (59)	26/76 (54)	27/77 (50)
			0.0001 *	0.3945	0.0061 **	0.0012 **
		Carcinoma, Hepatocellular	6/72 (52)	12/77 (57)	21/76 (50)	24/77 (50)
			0.0000 *	0.1404	0.0005 **	0.0000 **
		Hepatocellular_A+C	18/72 (53)	26/77 (60)	37/76 (56)	41/77 (55)
			0.0000 *	0.2045	0.0007 **	0.0000 **

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Rat Study: Rats (65/sex/dose) were dosed by oral gavage with ETC-1002 daily for up to 104 weeks. The respective ETC-1002 dose in the vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups was 0, 3, 10, or 30 mg/kg/day in females and males. The treatments for all rats were terminated at Weeks 104.

The survival analyses didn't show any statistically significant dose response relationship in mortality in males and females. The respective survival rates in the VC, LD, MD, or HD

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groups at the time they were terminated was 69%, 82%, 80%, or 75% in males and 48%, 52%, 57%, or 60% in females.

The tumor analysis (Table 1) showed statistically significant positive dose-response relationships in incidences for tumor types of hepatocellular adenoma or combined with carcinoma in liver, for follicular cell adenoma or combined with carcinoma in thyroid gland, and for islet cell adenoma combined with carcinoma in pancreas in male rats. The pairwise comparisons of incidence rates against the control were statistically significant for high dosed group only for the following tumor types: hepatocellular adenoma or combined with carcinoma in liver, follicular cell adenoma combined with carcinoma in thyroid gland, islet cell adenoma combined with carcinoma in pancreas. Of note, the nonclinical reviewer Dr. Haile considered the tumor types follicular cell adenoma or combined with carcinoma in thyroid gland in male rats as common tumors based on the historical control.

The tumor types of astrocytoma in brain in male rats had a statistically significant positive dose response relationship in tumor incidence. The pairwise comparisons of incidence rates of this tumor type against the control were not statistically significant for any dosed group.

Mouse Study: Mice (65/sex/dose) were dosed by oral gavage with ETC-1002 daily for up to 104 weeks. The respective ETC-1002 dose in the vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups was 0, 25, 75, or 150 mg/kg/day in males and females. The treatments for male mice and female mice were terminated at Weeks 104 and 101, respectively.

The survival analyses showed statistically significant dose response relationship in male mice only. Mortalities in male HD group and female MD group were significantly higher than that of the control group. The respective survival rates in the VC, LD, MD, or HD groups at the time they were terminated was 47%, 45%, 36%, or 26% in males and 34%, 35%, 20%, or 37% in females.

The tumor analysis (Table 1) showed statistically significant positive dose-response relationships in tumor incidence for the tumor types of hepatocellular adenoma, carcinoma, or combination of two in liver in male mice. The pairwise comparisons of incidence rates against the control for these tumor types were statistically significant for the mid and high dosed groups.

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2 Background

Bempedoic acid (ETC-1002) is a new chemical entity and a first in class novel inhibitor of adenosine triphosphate citrate lyase (ACL), developed for the treatment of primary hyperlipidemia. In the US, the development program for bempedoic acid was carried out under an Investigational New Drug (IND) Application number 106654, under the Division of Metabolic and Endocrine Products (DMEP). The original IND was submitted on 23 September 2009 and this IND is incorporated herein as reference. Esperion (the sponsor) hereby submitted the nonclinical studies rr-1002-500-035: "A 104-week oral carcinogenicity study in Wistar rats" and rr-1002-500-036: "A 104-week oral carcinogenicity study in mice" via submission NDA 2111616/SN-0001. The electronic tumor.xpt files were submitted on 4/3/2019 via NDA 211616/SN0006.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. Results of this review have been discussed with the nonclinical team.

3 Rat Study- rr-1002-500-035

Study Report: rr-1002-500-035.pdf (statistical report on page 944)
SAS data: tumor.xpt

This study was conducted to evaluate the carcinogenic potential of the test article, ETC-1002, after once daily oral gavage administration to male and female Wistar rats for up to 104 consecutive weeks. The test material was administered at doses of 0, 3, 10, or 30 mg/kg/day. This review refers these dose groups as the vehicle control (VC), low (LD), mid (MD), or high (HD) dose groups, respectively. There were 65 rats/sex/dose in the main study. All rats were terminated at Weeks 104.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test[12]. Any animal with accidental injury that caused death or unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. If this overall test was significant ($p < 0.05$) and there were more than two groups, then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

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Sponsor's concluded results: No test article-related cause of death occurred in either sex. In males there was not a clear most common cause of death/morbidity except for pituitary tumor having a slightly higher incidence in controls but not treated animals. In females the most common cause of death/morbidity was pituitary tumors across all groups.

3.1.2 Tumor Data Analysis

Neoplastic findings classified as fatal and incidental were processed using the death rate method and the prevalence method, respectively. The processing of incidental tumors was done by creating a single separate interval for the time following the experimental period (terminal sacrifice period) and by dividing the experimental period into the following fixed intervals [FDA's draft Guidance for industry. 2001]: weeks 1-52, weeks 53-78, weeks 79-92, and over week 92, and over week 92. Using the derived outcomes from the processing of both fatal and incidental tumors, a test statistic was built to perform a global survival-adjusted trend test on tumor data observed in a "mortality dependent" context [Peto et al, 1980].

All p-values are reported using upper-tailed test, unless otherwise indicated. Evaluation criteria (levels of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%) The evaluation criteria from the FDA are given in Table F (FDA).

Table F. Evaluation Criteria for Common and Rare Tumors

Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors will be tested at 0.005 and 0.025 significance levels, respectively	Common and rare tumors will be tested at 0.01 and 0.05 significance levels, respectively

Sponsor's concluded results: A test article-related increase in the incidence of hepatocellular adenoma in the liver and of follicular cell adenoma in the thyroid gland of male rats occurred at 30 mg/kg/day. There was no statistically significant increase in hepatocellular tumors in the females.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 4/3/2019 via NDA 211616/SN0006.

3.2.1 Survival Analysis

The survival distributions of rats in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions were tested using the log-rank test. The Kaplan-Meier curves for survival rates are

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given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 3A and 3B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 20 (31%), 12 (18%), 13 (20%), or 16 (25%) in male rats and 34 (52%), 31 (48%), 28 (43%), or 26 (40%) in female rats in the VC, LD, MD, and HD groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males and females.

3.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. Multiple testing adjustments currently follow the rule displayed in Table 12.6. [5, 6]

Table 12.6 Recommended decision rules (levels of significance) for controlling the overall false positive rates for various statistical tests performed and submission types

Submission type		Tumor type	Decision rule			
			Trend test alone	Pairwise test alone	Joint test	
					Trend test	Pairwise test
Standard 2 year study with two sexes and two species		Common	0.005	0.01	0.005	0.05
		Rare	0.025	0.05	0.025	0.10
Alternative ICH Studies (One 2-year study in one species and one short- or medium-term alternative study, two sexes)	Two-year study	Common	0.005	0.01	0.005	0.05
		Rare	0.025	0.05	0.025	0.10
	Short- or medium-term alternative study	Common	0.05	0.05	0.05	0.05
		Rare	0.05	0.05	0.05	0.05
Standard 2 year studies with two sexes and one species		Common	0.01	0.025	0.01	0.05
		Rare	0.05	0.10	0.05	0.10

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The adjusted levels of significance for testing a positive dose response in the 2-year rat study are 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 2-year rat study are 0.01 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group.

The tumor rates and the p-values of the tested tumor types are listed in Tables 5A and 5B in the appendix for male and female rats, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 in tests either for dose response relationships or for pairwise comparisons of treated groups and control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Controls in Rats

Sex	Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Male	Brain	Astrocytoma	0/65 (57)	0/65 (59)	0/65 (61)	3/65 (59)
			0.0150 *	NC	NC	0.1283
	Liver	Adenoma, Hepatocellular	0/65 (57)	0/65 (59)	1/65 (61)	7/65 (58)
			0.0001 *	NC	0.5169	0.0069 **
		Carcinoma, Hepatocellular	0/65 (57)	0/65 (59)	1/65 (61)	1/65 (58)
			0.1888	NC	0.5169	0.5043
		Hepatocellular_A+C	0/65 (57)	0/65 (59)	2/65 (61)	8/65 (58)
			0.0000 *	NC	0.2651	0.0032 **
	Pancreas	Adenoma, Islet Cell	1/65 (57)	3/65 (59)	0/65 (61)	7/65 (58)
			0.0063	0.3224	0.5169	0.0322
		Carcinoma, Islet Cell	0/65 (57)	1/65 (59)	1/65 (61)	2/65 (58)
			0.1200	0.5086	0.5169	0.2522
		Islet Cell_A+C	1/65 (57)	4/65 (59)	1/65 (61)	9/65 (58)
			0.0025 *	0.1930	0.7688	0.0088 **
	Thyroid Gland	Adenoma, Follicular Cell	0/65 (57)	2/65 (59)	4/65 (61)	9/65 (58)
			0.0005 *	0.2565	0.0680	0.0015 **
		Carcinoma, Follicular Cell	0/65 (57)	3/65 (59)	1/65 (61)	3/65 (59)
			0.1520	0.1283	0.5169	0.1283
		Follicular-Cell_A+C	0/65 (57)	5/65 (59)	5/65 (61)	12/65 (59)
			0.0004 *	0.0312	0.0340	0.0002 **
Female	Thyroid Gland	Carcinoma, Follicular Cell	1/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
			0.4509	0.5048	0.4902	0.2571
		Adenoma, Follicular Cell	4/65 (53)	2/65 (53)	5/65 (51)	9/65 (55)
			0.0207	0.6608	0.4754	0.1329
		Follicular-Cell_A+C	5/65 (53)	2/65 (53)	5/65 (51)	9/65 (55)
			0.0355	0.9437	0.6045	0.2168

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, the tumor types of hepatocellular adenoma or combined with carcinoma in liver in male rats were considered as rare tumors and to have a statistically significant positive dose response relationships

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($p<0.025$). The pairwise comparisons of incidence rates against the control were statistically significant for the high dosed group only.

The tumor types of follicular cell adenoma or combined with carcinoma in thyroid gland in male rats were considered as common tumors (according to the nonclinical reviewer Dr. Haile's review) and to have a statistically significant positive dose response relationships ($p<0.005$). The pairwise comparisons of incidence rates against the control were statistically significant for the high dosed group only ($p<0.01$).

The tumor types of islet cell adenoma combined with carcinoma in pancreas in male rats was considered as a common tumor and to have a statistically significant positive dose response relationship ($p<0.005$). The pairwise comparison of this tumor type incidence rates against the controls was statistically significant for high dosed group ($p<0.01$).

The tumor type of astrocytoma in brain in male rats was considered as a rare tumor and to have a statistically significant positive dose response relationship ($p=0.015<0.025$). The pairwise comparisons of this tumor type incidence rates against the controls were not statistically significant for any dosed group.

4 Mouse Study- rr-1002-500-036

Study Report: **rr-1002-500-036.pdf (statistical report on page 864)**
SAS data: **tumor.xpt**

This study was conducted to evaluate the carcinogenic potential of the test article, ETC-1002, after once daily oral gavage administration to male and female CD1 mice for up to 104 consecutive weeks. The test material was administered at doses of 0, 25, 75, or 150 mg/kg/day for male and female mice once daily for at least 104 weeks. This review refers these dose groups as the vehicle control (VC), low (LD), mid (MD), and high (HD) dose groups, respectively. There were 65 mice/sex/dose in the main study and 20 mice/sex/dose in toxicokinetic (TK) study. Surviving TK animals were transferred to the main study at Week 45. The treatment for male mice and female mice were terminated at Weeks 104 and 101, respectively.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

4.1 Sponsor's Analyses

4.1.1 Survival Analysis

The sponsor used the same survival analysis methods for the rat study in this mouse study.

Sponsor's concluded results: There was an increased incidence of animals with inflammation/septicemia as the cause of death in males at 150 mg/kg/day (10 out of 77 animals) when compared to controls (2 out of 72 animals). The origin of the inflammation was commonly found in the skin subcutis and liver. Of the ten animals, abscesses were observed microscopically in the liver alone in four animals, in the skin subcutis alone in three

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animals, and inflammation or abscess formation was observed within both the skin and liver in three animals. Similar effects were not observed in females. There has been a report of a high incidence of dermal-related lesions in control CD-1 male mice with secondary septicemia in animals exhibiting self-infliction trauma (scratching) to the head and neck region.

4.1.2 Tumor Data Analysis

The sponsor used the same tumor data analysis methods for the rat study in this mouse study.

Sponsor's findings: There was an ETC-1002-related increased incidence of benign hepatocellular adenoma and malignant hepatocellular carcinoma in the liver of males at 75 and 150 mg/kg day when compared to control animals. The increased incidences of the hepatocellular adenomas and carcinomas in males at 75 and 150 mg/kg/day were statistically significant. The increased incidences of hepatocellular carcinoma in males at 75 and 150 mg/kg/day were statistically significant. Statistical analysis of the hepatocellular adenomas and hepatocellular carcinomas combined showed increased incidences at 75 and 150 mg/kg/day that were statistically significant. Similar findings in the liver were not observed in females. All other differences in tumor incidences between control and ETC-1002-treated animals were not statistically significant and considered to be incidental or spontaneous.

4.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 4/3/2019 via NDA 211616/SN0006.

4.2.1 Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 38 (53%), 42 (55%), 49 (64%) or 57 (74%) in male mice and 48 (66%), 51 (65%), 59 (80%), or 47 (63%) in female mice in the VC, LD, MD, or HD groups, respectively. The survival analyses show a statistically significant dose response relationship in mortality in males only. Mortalities in male HD group and female MD group were significantly higher than that of the control group (Ps<0.05).

4.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of the water control group and the vehicle control group separately with each of the treated groups using the same method that was used for the rat study. The tumor rates and the p-values of the

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tested tumor types are listed in Tables 6A, and 6B in the appendix for male and female mice, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Controls in Mice

Sex	Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - C vs. L	75 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
Male	Liver	Adenoma, Hepatocellular	12/72 (52)	16/77 (59)	26/76 (54)	27/77 (50)
			0.0001 *	0.3945	0.0061 **	0.0012 **
		Carcinoma, Hepatocellular	6/72 (52)	12/77 (57)	21/76 (50)	24/77 (50)
			0.0000 *	0.1404	0.0005 **	0.0000 **
		Hepatocellular_A+C	18/72 (53)	26/77 (60)	37/76 (56)	41/77 (55)
			0.0000 *	0.2045	0.0007 **	0.0000 **
	Multicentric	Hemangioma	3/72 (53)	1/77 (56)	1/76 (47)	4/77 (46)
	Neoplasm		0.1696	0.7116	0.6445	0.4206
		Hemangiosarcoma	9/72 (52)	7/77 (58)	15/76 (51)	13/77 (47)
			0.0297	0.6944	0.1111	0 1599
		Hemangioma/	12/72 (53)	8/77 (58)	16/76 (51)	17/77 (49)
		Hemangiosarcoma	0.0166	0.9279	0.2171	0 1295
Female	Mammary	Adenocarcinoma	0/73 (42)	3/78 (45)	6/74 (36)	1/75 (43)
	Gland		0.3959	0.1339	0.0076 **	0 5059

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, the tumor types of hepatocellular adenoma, carcinoma, or combination of the two in liver in male mice were considered as common tumors and to have statistically significant positive dose response relationships ($p<0.005$). The pairwise comparisons of incidence rates against the control for these tumor types were statistically significant for the mid and high dosed groups ($p<0.01$).

The tumor type of adenocarcinoma in mammary gland in female mice was considered as a rare tumor and the pairwise comparison of this tumor type incidence rates against the controls was statistically significant for mid dosed group ($p=0.0076<0.05$); there was no statistically significant positive dose-response relationship among treatment groups in this tumor type.

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Karl Lin, Ph.D., Team Leader, Biometrics-6
cc:
Dr. Lydia Haile
Dr. Calvin Elmore
Dr. Yi Tsong

File Name: NDA211616Carcin

Dr. Karl Lin

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5 Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	1	1.54	2	3.08	1	1 54	1	1.54
53 - 78	3	6.15					5	9.23
79 - 92	10	21.54	7	13.85	4	7.69	3	13.85
93 - 104	6	30.77	3	18.46	8	20.00	7	24.62
Terminal sacrifice	45	69.23	53	81.54	52	80.00	49	75.38
Total	65		65		65		65	

** All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	1	1.54	2	3.08	1	1 54	2	3.08
53 - 78	10	16.92	9	16.92	13	21.54	5	10.77
79 - 92	9	30.77	6	26.15	9	35.38	10	26.15
93 - 104	14	52.31	14	47.69	5	43.08	9	40.00
Terminal sacrifice	31	47.69	34	52.31	37	56.92	39	60.00
Total	65		65		65		65	

** All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 2A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	9	12.50	6	7.79	9	11.84	13	16.88
53 - 78	12	29.17	11	22.08	18	35.53	18	40.26
79 - 92	5	36.11	12	37.66	12	51.32	11	54.55
93 - 104	12	52.78	12	53.25	10	64.47	15	74.03
Accidental Death			1	1.30				
Terminal sacrifice	34	47.22	35	45.45	27	35.53	20	25.97
Total	72		77		76		77	

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Table 2B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	8	10.96	9	11.54	11	14.86	13	17.33
53 - 78	18	35.62	23	41.03	33	59.46	18	41.33
79 - 92	13	53.42	11	55.13	6	67.57	8	52.00
93 - 104	8	64.38	8	65.38	9	79.73	8	62.67
Accidental Death	1	1.37						
Terminal sacrifice	25	34.25	27	34.62	15	20.27	28	37.33
Total	73		78		74		75	

** All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 3A: Intercurrent Mortality Comparison in Male Rats

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.8866	0.1130	0.1202	0.4340
Homogeneity (Log-Rank)	0.3048	0.1120	0.1182	0.4311

Table 3B: Intercurrent Mortality Comparison in Female Rats

Test	**All Dose Groups**	**Vehicle Control vs. Low**	**Vehicle Control vs. Mid**	**Vehicle Control vs. High**
Dose-Response (Likelihood Ratio)	0.2297	0.5863	0.5070	0.2099
Homogeneity (Log-Rank)	0.6512	0.5830	0.5045	0.2072

Table 4A: Intercurrent Mortality Comparison in Male Mice

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.0015	0.9593	0.1289	0.0088
Homogeneity (Log-Rank)	0.0109	0.9590	0.1263	0.0082

Table 4B: Intercurrent Mortality Comparison in Female Mice

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.8027	0.9240	0.0161	0.9345
Homogeneity (Log-Rank)	0.0226	0.9233	0.0148	0.9341

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Table 5A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Adipose Tissue, Brown	Hibernoma	0/65 (57)	0/65 (59)	1/65 (62)	0/65 (58)
		0.2458	NC	0.5210	NC
Adrenal Glands	Adenoma, Cortical	3/65 (57)	5/65 (60)	4/65 (62)	2/65 (58)
		0.7851	0.3875	0.5471	0 5083
	Carcinoma, Cortical	3/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.9863	0.8846	0.8904	0.8815
	Cortical_A+C	5/65 (57)	5/65 (60)	4/65 (62)	2/65 (58)
		0.9036	0.6609	0.7949	0 9459
	Ganglioneuroma	0/65 (57)	0/65 (59)	0/65 (61)	1/65 (58)
		0.2468	NC	NC	0 5043
	Pheochromocytoma	3/65 (58)	0/65 (59)	1/65 (61)	2/65 (58)
		0.4233	0.8814	0.7095	0 5000
Brain	Astrocytoma	0/65 (57)	0/65 (59)	0/65 (61)	3/65 (59)
		0.0150 *	NC	NC	0 1283
	Granular Cell Tumor	1/65 (57)	3/65 (59)	0/65 (61)	3/65 (59)
		0.2354	0.3224	0.5169	0 3224
Cavity, Abdominal	Sarcoma, Undifferentiated	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
	Schwannoma	1/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.6310	0.5086	0.2651	0 5043
Cavity, Oral	Hemangiosarcoma	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
Cavity, Thoracic	Schwannoma	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
Coagulating Glands	Sarcoma, Undifferentiated	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
Epididymides	Mesothelioma	1/65 (57)	1/65 (59)	0/65 (61)	1/65 (58)
		0.5312	0.2565	0.5169	0 2522
Hard Palate	Carcinoma, Sebaceous Cell	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
	Carcinoma, Squamous Cell	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
Head	Carcinoma, Sebaceous Cell	0/65 (57)	1/65 (60)	0/65 (61)	0/65 (58)
		0.5042	0.5128	NC	NC
	Schwannoma	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
Heart	Schwannoma	1/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.6310	0.5086	0.2651	0 5043
Kidneys	Hemangiosarcoma	0/65 (57)	0/65 (59)	1/65 (62)	0/65 (58)
		0.2458	NC	0.5210	NC
	Renal Sarcoma	0/65 (57)	1/65 (60)	0/65 (61)	0/65 (58)
		0.5042	0.5128	NC	NC

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Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Liver	Adenoma, Hepatocellular	0/65 (57)	0/65 (59)	1/65 (61)	7/65 (58)
		0.0001 *	NC	0.5169	0.0069 **
	Carcinoma, Hepatocellular	0/65 (57)	0/65 (59)	1/65 (61)	1/65 (58)
		0.1888	NC	0.5169	0 5043
	Hepatocellular_A+C	0/65 (57)	0/65 (59)	2/65 (61)	8/65 (58)
		0.0000 *	NC	0.2651	0.0032 **
	Sarcoma, Undifferentiated	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
Lung	Carcinoma, Squamous Cell	0/65 (57)	1/65 (60)	0/65 (61)	0/65 (58)
		0.5042	0.5128	NC	NC
	Sarcoma, Undifferentiated	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
Lymph Node, Mandibular	Schwannoma	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
Lymph Node, Mesenteric	Hemangiosarcoma	2/65 (57)	2/65 (59)	6/65 (62)	3/65 (59)
		0.3548	0.3224	0.1652	0 5164
	Schwannoma	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
Mammary Gland	Adenocarcinoma	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
Multicentric Neoplasm	Leukemia, Large Granular	0/65 (57)	0/65 (59)	0/65 (61)	1/65 (59)
	Lymphoma	0.2500	NC	NC	0 5086
	Lymphoma	2/65 (58)	3/65 (60)	4/65 (62)	4/65 (60)
		0.2526	0.5162	0.3720	0 3559
Nose, Level A	Adenoma	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
	Ameloblastic/Odontoblastic	1/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
	Tumor	0.6310	0.5086	0.2651	0 5043
Nose, Level C	Papilloma	0/65 (57)	0/65 (59)	0/65 (61)	1/65 (58)
		0.2468	NC	NC	0 5043
	Schwannoma	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
Nose, Level D	Carcinoma, Squamous Cell	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
Pancreas	Adenoma, Acinar Cell	0/65 (57)	0/65 (59)	0/65 (61)	2/65 (58)
		0.0601	NC	NC	0 2522
	Adenoma, Islet Cell	1/65 (57)	3/65 (59)	0/65 (61)	7/65 (58)
		0.0063	0.3224	0.5169	0.0322
	Carcinoma, Islet Cell	0/65 (57)	1/65 (59)	1/65 (61)	2/65 (58)
		0.1200	0.5086	0.5169	0 2522
	Isletcell_A+C	1/65 (57)	4/65 (59)	1/65 (61)	9/65 (58)
		0.0025 *	0.1930	0.7688	0.0088 **
	Sarcoma, Undifferentiated	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
Parathyroid Glands	Adenoma	2/65 (57)	2/65 (59)	1/65 (61)	0/65 (58)

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Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
		0.9202	0.3224	0.5256	0.7565
	Carcinoma, C-Cell	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
	Carcinoma, Follicular Cell	0/65 (57)	0/65 (59)	0/65 (61)	1/65 (58)
		0.2468	NC	NC	0 5043
Pituitary Gland	Adenoma, Pars Distalis	31/65 (61)	29/65 (62)	26/65 (62)	22/65 (60)
		0.9410	0.6057	0.7901	0 9172
	Adenoma, Pars Intermedia	3/65 (57)	1/65 (59)	6/65 (61)	0/65 (58)
		0.8879	0.7037	0.2803	0.8815
Prostate Gland	Adenoma	6/65 (58)	2/65 (60)	1/65 (61)	1/65 (58)
		0.9605	0.8748	0.9506	0 9432
	Sarcoma, Undifferentiated	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
Salivary Gland, Mandibular	Adenocarcinoma	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
Salivary Gland, Parotid	Adenocarcinoma	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
	Schwannoma	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
Seminal Vesicles	Sarcoma, Undifferentiated	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
Skeletal Muscle	Sarcoma, Undifferentiated	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
	Schwannoma	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
Skin	Adenoma, Basal Cell	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
	Carcinoma, Squamous Cell	0/65 (57)	1/65 (60)	0/65 (61)	0/65 (58)
		0.5042	0.5128	NC	NC
	Hair Follicle Tumor	0/65 (57)	0/65 (59)	0/65 (61)	1/65 (58)
		0.2468	NC	NC	0 5043
	Keratoacanthoma	2/65 (57)	2/65 (59)	0/65 (61)	1/65 (58)
		0.7234	0.3224	0.7688	0 5066
	Papilloma, Fibrous	0/65 (57)	0/65 (59)	0/65 (61)	1/65 (58)
		0.2468	NC	NC	0 5043
	Papilloma, Squamous Cell	0/65 (57)	1/65 (60)	1/65 (61)	1/65 (58)
		0.2975	0.5128	0.5169	0 5043
Skin, Subcutis	Fibroma	2/65 (57)	2/65 (60)	3/65 (62)	0/65 (58)
		0.8943	0.3289	0.5400	0.7565
	Hemangioma	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
	Hemangiosarcoma	0/65 (57)	1/65 (59)	1/65 (62)	0/65 (58)
		0.5001	0.5086	0.5210	NC
	Lipoma	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
	Liposarcoma	0/65 (57)	0/65 (59)	1/65 (62)	0/65 (58)
		0.2458	NC	0.5210	NC

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Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
	Rhabdomyosarcoma	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
	Schwannoma	0/65 (57)	2/65 (59)	0/65 (61)	1/65 (59)
		0.4447	0.2565	NC	0 5086
Spleen	Hemangiosarcoma	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.7574	0.5086	0.5169	0 5043
	Leiomyosarcoma	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
Stomach, Glandular	Leiomyosarcoma	0/65 (57)	0/65 (59)	0/65 (61)	1/65 (58)
		0.2468	NC	NC	0 5043
Testes	Adenoma, Leydig Cell	1/65 (57)	0/65 (59)	1/65 (61)	2/65 (58)
		0.1664	0.5086	0.2651	0 5066
	Mesothelioma	1/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.8196	0.2565	0.5169	0 5043
Thymus	Carcinoma, Squamous Cell	0/65 (57)	1/65 (59)	0/65 (61)	0/65 (58)
		0.5064	0.5086	NC	NC
	Thymoma	2/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.9420	0.7607	0.7688	0.7565
Thyroid Gland	Adenoma, C-Cell	8/65 (58)	13/65 (60)	9/65 (62)	9/65 (58)
		0.5950	0.1905	0.5596	0 5000
	Carcinoma, C-Cell	1/65 (57)	2/65 (60)	0/65 (61)	0/65 (58)
		0.8956	0.5194	0.5169	0 5043
	C-Cell_a+c	9/65 (58)	15/65 (61)	9/65 (62)	9/65 (58)
		0.7287	0.1576	0.6590	NC
	Adenoma, Follicular Cell	0/65 (57)	2/65 (59)	4/65 (61)	9/65 (58)
		0.0005 *	0.2565	0.0680	0.0015 **
	Carcinoma, Follicular Cell	0/65 (57)	3/65 (59)	1/65 (61)	3/65 (59)
		0.1520	0.1283	0.5169	0 1283
	Follicular-Cell_A+C	0/65 (57)	5/65 (59)	5/65 (61)	12/65 (59)
		0.0004 *	0.0312 **	0.0340 **	0.0002 **
Urinary Bladder	Sarcoma, Undifferentiated	0/65 (57)	0/65 (59)	1/65 (61)	0/65 (58)
		0.2468	NC	0.5169	NC
Zymbal`s Gland	Carcinoma, Sebaceous Cell	2/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		0.9420	0.7607	0.7688	0.7565
Whole Body	Hemangioma	1/65 (57)	0/65 (59)	0/65 (61)	0/65 (58)
		1.0000	1.0000	1.0000	1.0000
	Hemangiosarcoma	4/65 (57)	3/65 (59)	8/65 (62)	3/65 (59)
		0.6234	0.7948	0.2247	0.7948
	Hemangioma/	5/65 (57)	3/65 (59)	8/65 (62)	3/65 (59)
	Hemangiosarcoma	0.7014	0.8751	0.3362	0.8751
	Liposarcoma	0/65 (57)	0/65 (59)	1/65 (62)	0/65 (58)
		0.5085	NC	0.5210	NC

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

File Name: NDA211616Carcin

Table 5B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	30 mg High (H) P - H vs. C
Adrenal Glands	Adenoma, Cortical	2/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.5464	0.7571	0.7426	0.5143
	Carcinoma, Cortical	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
	Ganglioneuroma	0/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.2584	NC	0.4902	NC
	Liposarcoma	0/65 (52)	1/65 (54)	0/65 (50)	0/65 (54)
		0.4952	0.5094	NC	NC
Bone Marrow, Femur	Hemangioma	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
Brain	Astrocytoma	0/65 (52)	1/65 (53)	0/65 (50)	1/65 (54)
		0.3217	0.5048	NC	0.5094
	Carcinoma, Pars Distalis	2/65 (52)	1/65 (53)	2/65 (50)	2/65 (54)
		0.4150	0.5072	0.6763	0.3233
	Granular Cell Tumor	0/65 (52)	2/65 (53)	0/65 (50)	1/65 (54)
		0.4472	0.2524	NC	0.5094
	Oligodendroglioma	0/65 (52)	1/65 (53)	0/65 (50)	0/65 (54)
		0.4976	0.5048	NC	NC
	Reticulosis	0/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.2584	NC	NC	0.5094
Cavity, Abdominal	Adenocarcinoma	0/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.2584	NC	NC	0.5094
	Adenocarcinoma (Primary Site	1/65 (52)	0/65 (53)	2/65 (50)	0/65 (54)
		0.6505	0.5048	0.4851	0.5094
	Fibroma	0/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.2584	NC	0.4902	NC
	Leiomyosarcoma	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
	Liposarcoma	0/65 (52)	1/65 (54)	0/65 (50)	0/65 (54)
		0.4952	0.5094	NC	NC
	Schwannoma	2/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.5464	0.7571	0.7426	0.5143
Cavity, Thoracic	Schwannoma	0/65 (52)	0/65 (53)	1/65 (51)	0/65 (54)
		0.2571	NC	0.4951	NC
Clitoral Glands	Adenocarcinoma	1/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.4509	0.5048	0.4902	0.2571
	Adenoma	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
Eyes	Melanoma, Amelanotic	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
Hard Palate	Carcinoma, Squamous Cell	0/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.2584	NC	NC	0.5094
Heart	Schwannoma	0/65 (52)	0/65 (53)	1/65 (51)	0/65 (54)
		0.2571	NC	0.4951	NC
Kidneys	Adenocarcinoma	1/65 (52)	0/65 (53)	1/65 (50)	1/65 (54)

File Name: NDA211616Carcin

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	30 mg High (H) P - H vs. C
		0.3976	0.5048	0.7426	0.2571
	Carcinoma, Transitional Cell	0/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.2584	NC	0.4902	NC
	Liposarcoma	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
Liver	Adenocarcinoma	1/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.6292	0.5048	0.7426	0.5094
	Adenoma, Hepatocellular	0/65 (52)	1/65 (53)	3/65 (51)	1/65 (54)
		0.3952	0.5048	0 1178	0.5094
	Hemangiosarcoma	0/65 (52)	0/65 (53)	2/65 (51)	1/65 (54)
		0.2083	NC	0 2427	0.5094
	Liposarcoma	0/65 (52)	1/65 (54)	0/65 (50)	0/65 (54)
		0.4952	0.5094	NC	NC
Lung	Adenocarcinoma	0/65 (52)	0/65 (53)	3/65 (51)	0/65 (54)
		0.5450	NC	0 1178	NC
	Carcinoma, Cortical	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
	Hemangiosarcoma	0/65 (52)	0/65 (53)	1/65 (51)	0/65 (54)
		0.2571	NC	0.4951	NC
Lymph Node, Iliac	Adenocarcinoma	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
Lymph Node, Mediastinal	Adenocarcinoma	0/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.2584	NC	0.4902	NC
Lymph Node, Mesenteric	Hemangiosarcoma	0/65 (52)	4/65 (54)	1/65 (50)	1/65 (54)
		0.6537	0.0637	0.4902	0.5094
Mammary Gland	Adenocarcinoma	5/65 (53)	1/65 (53)	6/65 (52)	1/65 (54)
		0.8750	0.8974	0.4864	0.9016
	Fibroadenoma	9/65 (54)	5/65 (54)	9/65 (52)	4/65 (54)
		0.8713	0.8045	0 5672	0.8819
Multicentric Neoplasm	Lymphoma	6/65 (52)	3/65 (53)	5/65 (51)	4/65 (54)
		0.6206	0.7654	0.4862	0.6532
	Sarcoma, Histiocytic	3/65 (53)	0/65 (53)	0/65 (50)	1/65 (54)
		0.6986	0.8786	0.8675	0.6981
Ovaries	Hemangiosarcoma	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
	Sex-Cord/Stromal Tumor	2/65 (52)	1/65 (53)	3/65 (50)	3/65 (54)
		0.2443	0.5072	0.4812	0.5180
Pancreas	Adenocarcinoma	1/65 (52)	0/65 (53)	1/65 (50)	1/65 (54)
		0.3976	0.5048	0.7426	0.2571
	Adenoma, Islet Cell	1/65 (52)	1/65 (53)	0/65 (50)	0/65 (54)
		0.8122	0.2524	0.4902	0.5094
	Carcinoma, Islet Cell	1/65 (52)	1/65 (53)	0/65 (50)	0/65 (54)
		0.8122	0.2524	0.4902	0.5094
	Schwannoma	0/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.2584	NC	NC	0.5094

Reference ID: 4465565

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	30 mg High (H) P - H vs. C
Pituitary Gland	Adenoma, Pars Distalis	51/65 (59)	47/65 (62)	49/65 (60)	37/65 (58)
		0.9957	0.8963	0.6769	0.9960
	Adenoma, Pars Intermedia	0/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.2584	NC	0.4902	NC
	Carcinoma, Pars Distalis	2/65 (52)	1/65 (53)	2/65 (50)	2/65 (54)
		0.4150	0.5072	0.6763	0.3233
Salivary Gland, Mandibular	Adenocarcinoma	0/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.2584	NC	NC	0.5094
Salivary Gland, Parotid	Adenoma	0/65 (52)	0/65 (53)	0/65 (50)	2/65 (54)
		0.0658	NC	NC	0.2571
Skeletal Muscle, Diaphragm	Adenocarcinoma	0/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.2584	NC	0.4902	NC
Skin	Carcinoma, Squamous Cell	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
Skin, Subcutis	Fibrosarcoma	0/65 (52)	1/65 (53)	0/65 (50)	0/65 (54)
		0.4976	0.5048	NC	NC
	Hemangioma	0/65 (52)	0/65 (53)	1/65 (51)	0/65 (54)
		0.2571	NC	0.4951	NC
Small Intestine, Ileum	Liposarcoma	0/65 (52)	1/65 (54)	0/65 (50)	0/65 (54)
		0.4952	0.5094	NC	NC
Small Intestine, Jejunum	Leiomyoma	0/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.2584	NC	NC	0.5094
Spleen	Adenocarcinoma	0/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.2584	NC	0.4902	NC
	Liposarcoma	0/65 (52)	1/65 (54)	0/65 (50)	0/65 (54)
		0.4952	0.5094	NC	NC
Stomach, Nonglandular	Fibrosarcoma	0/65 (52)	1/65 (53)	0/65 (50)	0/65 (54)
		0.4976	0.5048	NC	NC
Thymus	Leiomyoma	0/65 (52)	1/65 (53)	0/65 (50)	0/65 (54)
		0.4976	0.5048	NC	NC
	Thymoma	0/65 (52)	0/65 (53)	1/65 (50)	1/65 (54)
		0.1901	NC	0.4902	0.5094
Thyroid Gland	Adenoma, C-Cell	10/65 (52)	9/65 (54)	3/65 (50)	4/65 (54)
		0.9725	0.5365	0 9578	0.9354
	Carcinoma, C-Cell	2/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.9390	0.7571	0.7426	0.7617
	C-Cell_a+c	12/65 (52)	9/65 (54)	3/65 (50)	4/65 (54)
		0.9894	0.8580	0 9975	0.9950
	Adenoma, Follicular Cell	4/65 (53)	2/65 (53)	5/65 (51)	9/65 (55)
		0.0207	0.6608	0.4754	0.1329
	Carcinoma, Follicular Cell	1/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.4509	0.5048	0.4902	0.2571
	Follicular-Cell_a+c	5/65 (53)	2/65 (53)	5/65 (51)	9/65 (55)
		0.0355	0.9437	0.6045	0.2168

File Name: NDA211616Carcin

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	30 mg High (H) P - H vs. C
Urinary Bladder	Adenocarcinoma	2/65 (52)	0/65 (53)	1/65 (51)	0/65 (54)
		0.8323	0.7571	0.4926	0.7617
Uterus With Cervix	Adenocarcinoma	4/65 (52)	0/65 (53)	5/65 (51)	4/65 (54)
		0.2403	0.9434	0.4876	0.3793
	Adenoma	1/65 (52)	1/65 (53)	1/65 (51)	0/65 (54)
		0.7400	0.2524	0.7476	0.5094
	Carcinoma, Squamous Cell	0/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.2584	NC	0.4902	NC
	Fibrosarcoma	0/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.2584	NC	NC	0.5094
	Granular Cell Tumor	1/65 (52)	0/65 (53)	0/65 (50)	3/65 (54)
		0.0539	0.5048	0.4902	0.3233
	Hemangiosarcoma	3/65 (52)	0/65 (53)	0/65 (50)	2/65 (54)
		0.4240	0.8821	0.8713	0.5180
	Leiomyosarcoma	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
	Liposarcoma	0/65 (52)	1/65 (54)	0/65 (50)	0/65 (54)
		0.4952	0.5094	NC	NC
	Polyp, Endometrial Stromal	7/65 (53)	10/65 (54)	5/65 (52)	10/65 (55)
		0.3067	0.3138	0.6062	0.3289
	Polyp, Glandular	3/65 (52)	0/65 (53)	0/65 (50)	1/65 (54)
		0.7015	0.8821	0.8713	0.7053
	Sarcoma, Endometrial Stromal	0/65 (52)	1/65 (54)	0/65 (50)	0/65 (54)
		0.4952	0.5094	NC	NC
	Schwannoma	1/65 (52)	1/65 (53)	2/65 (52)	3/65 (54)
		0.1327	0.2524	0 5000	0.3233
Vagina	Carcinoma, Squamous Cell	0/65 (52)	0/65 (53)	1/65 (50)	0/65 (54)
		0.2584	NC	0.4902	NC
	Granular Cell Tumor	1/65 (52)	0/65 (53)	0/65 (50)	0/65 (54)
		0.7512	0.5048	0.4902	0.5094
	Schwannoma	1/65 (52)	1/65 (53)	0/65 (50)	1/65 (54)
		0.5464	0.2524	0.4902	0.2571
Zymbal`s Gland	Carcinoma, Sebaceous Cell	0/65 (52)	1/65 (53)	1/65 (51)	0/65 (54)
		0.5072	0.5048	0.4951	NC

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 6A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Males Mice

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - C vs. L	75 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
Adrenal Glands	Adenoma, Cortical	0/72 (51)	0/77 (56)	1/76 (47)	1/77 (45)
		0.1576	NC	0.4796	0.4687
	Adenoma, Subcapsular Cell	8/72 (52)	2/77 (56)	0/76 (47)	0/77 (45)
		0.9999	0.9643	0.9956	0.9948
	Carcinoma, Subcapsular Cell	1/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7437	0.5234	0.4796	0.4688
	Subcapsular Cell_A+C	8/72 (52)	2/77 (56)	0/76 (47)	0/77 (45)

File Name: NDA211616Carcin

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - C vs. L	75 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
		1.0000	0.9943	1.0000	1.0000
	Pheochromocytoma	0/72 (51)	0/77 (56)	0/76 (47)	1/77 (45)
		0.2261	NC	NC	0.4687
Bone, Mandible	Osteosarcoma	0/72 (51)	1/77 (57)	0/76 (47)	0/77 (45)
		0.4600	0.5278	NC	NC
Cavity, Abdominal	Adenocarcinoma (Primary Site	1/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7437	0.5234	0.4796	0.4688
	Sarcoma, Undifferentiated	0/72 (51)	0/77 (56)	1/76 (47)	0/77 (45)
		0.4623	NC	0.4796	NC
Cavity, Thoracic	Carcinoma, Bronchiolar Alveol	2/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.9353	0.7752	0.7317	0.7204
Ears	Fibrosarcoma	0/72 (51)	0/77 (56)	0/76 (47)	1/77 (45)
		0.2261	NC	NC	0.4687
Epididymides	Carcinoma, Bronchiolar Alveol	1/72 (52)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7400	0.5185	0.4747	0.4639
Gallbladder	Adenoma	1/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7437	0.5234	0.4796	0.4688
Harderian Glands	Adenocarcinoma	0/72 (51)	4/77 (58)	3/76 (48)	1/77 (45)
		0.4975	0.0763	0.1103	0.4687
	Adenoma	9/72 (53)	10/77 (57)	12/76 (49)	8/77 (48)
		0.4705	0.5698	0.2445	0.4105
	Adenoma/Adenocarcinoma	9/72 (53)	14/77 (59)	14/76 (50)	9/77 (48)
		0.4775	0.2592	0.1345	0.5101
Heart	Carcinoma, Bronchiolar Alveol	2/72 (51)	1/77 (56)	0/76 (47)	0/77 (45)
		0.9287	0.5354	0.7317	0.7204
Kidneys	Carcinoma, Bronchiolar Alveol	1/72 (52)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7400	0.5185	0.4747	0.4639
Liver	Adenoma, Hepatocellular	12/72 (52)	16/77 (59)	26/76 (54)	27/77 (50)
		0.0001 *	0.3945	0.0061 **	0.0012 **
	Carcinoma, Hepatocellular	6/72 (52)	12/77 (57)	21/76 (50)	24/77 (50)
		0.0000 *	0.1404	0.0005 **	0.0000 **
	Hepatocellular_A+C	18/72 (53)	26/77 (60)	37/76 (56)	41/77 (55)
		0.0000 *	0.2045	0.0007 **	0.0000 **
	Liposarcoma	0/72 (51)	0/77 (56)	0/76 (47)	1/77 (45)
		0.2261	NC	NC	0.4687
Lung	Adenoma, Bronchiolar Alveolar	13/72 (53)	9/77 (57)	6/76 (49)	9/77 (45)
		0.6370	0.8176	0.9102	0.6135
	Carcinoma, Bronchiolar	11/72 (53)	8/77 (57)	8/76 (48)	9/77 (46)
	Alveolar	0.4523	0.7514	0.6052	0.4573
	Bronchiolar Alveolar_A+C	21/72 (55)	15/77 (58)	13/76 (50)	18/77 (46)
		0.3360	0.9462	0.9389	0.5423
	Carcinoma, Hepatocellular	1/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7437	0.5234	0.4796	0.4688
	Osteosarcoma	0/72 (51)	1/77 (57)	0/76 (47)	0/77 (45)

Reference ID: 4465565

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - C vs. L	75 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
		0.4600	0.5278	NC	NC
	Sarcoma, Undifferentiated	0/72 (51)	0/77 (56)	1/76 (47)	0/77 (45)
		0.4623	NC	0.4796	NC
Lymph Node, Axillary	Fibrosarcoma	0/72 (51)	0/77 (56)	1/76 (48)	0/77 (45)
		0.4650	NC	0.4848	NC
Lymph Node, Hepatic	Adenocarcinoma	1/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7437	0.5234	0.4796	0.4688
Lymph Node, Iliac	Adenocarcinoma	1/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7437	0.5234	0.4796	0.4688
Lymph Node, Mediastinal	Carcinoma, Bronchiolar Alveol	1/72 (52)	1/77 (56)	0/76 (47)	0/77 (45)
		0.7870	0.2665	0.4747	0.4639
Multicentric Neoplasm	Hemangioma	3/72 (53)	1/77 (56)	1/76 (47)	4/77 (46)
		0.1696	0.7116	0.6445	0.4206
	Hemangiosarcoma	9/72 (52)	7/77 (58)	15/76 (51)	13/77 (47)
		0.0297	0.6944	0.1111	0.1599
	Lymphoma	2/72 (53)	5/77 (58)	6/76 (49)	6/77 (46)
		0.0682	0.2579	0.1107	0.0935
	Mast Cell Tumor	0/72 (51)	1/77 (56)	0/76 (47)	1/77 (45)
		0.2855	0.5234	NC	0.4687
	Sarcoma, Histiocytic	1/72 (51)	1/77 (56)	1/76 (48)	0/77 (45)
		0.6979	0.2716	0.7372	0.4688
Nose, Level A	Odontoma	1/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7437	0.5234	0.4796	0.4688
Pancreas	Adenoma, Islet Cell	1/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7437	0.5234	0.4796	0.4688
Pituitary Gland	Adenoma, Pars Distalis	1/72 (51)	0/77 (56)	0/76 (47)	1/77 (45)
		0.4569	0.5234	0.4796	0.7204
Preputial Glands	Adenoma	0/72 (51)	0/77 (56)	0/76 (47)	1/77 (45)
		0.2261	NC	NC	0.4687
Prostate Gland	Adenoma	0/72 (51)	0/77 (56)	0/76 (47)	1/77 (45)
		0.2261	NC	NC	0.4687
Skin, Subcutis	Carcinoma, Squamous Cell	0/72 (51)	0/77 (56)	1/76 (48)	0/77 (45)
		0.4650	NC	0.4848	NC
	Fibrosarcoma	0/72 (51)	0/77 (56)	1/76 (48)	1/77 (45)
		0.1583	NC	0.4848	0.4687
	Fibrous Histiocytoma	0/72 (51)	0/77 (56)	1/76 (48)	0/77 (45)
		0.4650	NC	0.4848	NC
	Keratoacanthoma	0/72 (51)	0/77 (56)	0/76 (47)	1/77 (45)
		0.2261	NC	NC	0.4687
	Sarcoma, Undifferentiated	0/72 (51)	0/77 (56)	0/76 (47)	1/77 (45)
		0.2261	NC	NC	0.4687
Stomach, Glandular	Adenoma	2/72 (51)	2/77 (57)	0/76 (47)	0/77 (45)
		0.9463	0.3522	0.7317	0.7204

Reference ID: 4465565

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - C vs. L	75 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
Testes	Adenoma, Interstitial Cell	3/72 (51)	1/77 (57)	2/76 (47)	2/77 (45)
		0.4994	0.7319	0.4610	0.4403
	Adenoma, Rete Testis	1/72 (51)	0/77 (56)	0/76 (47)	0/77 (45)
		0.7437	0.5234	0.4796	0.4688
Thyroid Gland	Adenoma, Follicular Cell	2/72 (52)	0/77 (56)	0/76 (47)	1/77 (45)
		0.5496	0.7705	0.7267	0.4454
Whole Body	Hemangioma	3/72 (53)	1/77 (56)	1/76 (47)	4/77 (46)
		0.1696	0.9474	0.9253	0.4206
	Hemangiosarcoma	9/72 (52)	7/77 (58)	15/76 (51)	13/77 (47)
		0.0297	0.8528	0.1111	0.1599
	Hemangioma/	12/72 (53)	8/77 (58)	16/76 (51)	17/77 (49)
	Hemangiosarcoma	0.0166	0.9279	0.2171	0.1295

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 6B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - L vs. C	75 mg Mid (M) P - M vs. C	150 mg High (H) P - H vs. C
Adrenal Glands	Adenoma, Subcapsular Cell	1/73 (42)	3/78 (45)	2/74 (33)	3/75 (43)
		0.2620	0.3347	0.4092	0.3169
	Carcinoma, Subcapsular Cell	1/73 (42)	0/78 (44)	0/74 (33)	1/75 (42)
		0.4959	0.5116	0.4400	NC
	Subcapsular Cell_A+C	2/73 (42)	3/78 (45)	2/74 (33)	4/75 (43)
		0.2372	0.5331	0.5962	0.3493
	Pheochromocytoma	2/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.9332	0.7644	0.6897	0.7530
Brain	Astrocytoma	0/73 (42)	1/78 (45)	0/74 (33)	0/75 (42)
		0.4630	0.5172	NC	NC
Cavity, Abdominal	Adenocarcinoma	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
Ears	Fibrosarcoma	0/73 (42)	0/78 (44)	0/74 (33)	1/75 (43)
		0.2654	NC	NC	0.5059
Harderian Glands	Adenocarcinoma	1/73 (42)	0/78 (44)	0/74 (33)	2/75 (42)
		0.1994	0.5116	0.4400	0.5000
	Adenoma	3/73 (42)	7/78 (45)	2/74 (33)	6/75 (43)
		0.3279	0.1867	0.3855	0.2535
	Adenoma/Adenocarcinoma	4/73 (42)	7/78 (45)	2/74 (33)	8/75 (43)
		0.1940	0.3021	0.8345	0.1871
Head	Osteosarcoma	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
Kidneys	Adenoma, Renal Tubule	1/73 (42)	0/78 (44)	0/74 (33)	1/75 (43)
		0.5021	0.5116	0.4400	0.2529

File Name: NDA211616Carcin

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - L vs. C	75 mg Mid (M) P - M vs. C	150 mg High (H) P - H vs. C
	Renal Mesenchymal Tumor	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
Larynx	Fibrosarcoma	0/73 (42)	0/78 (44)	0/74 (33)	1/75 (43)
		0.2654	NC	NC	0.5059
Liver	Adenoma, Hepatocellular	3/73 (42)	2/78 (45)	3/74 (33)	3/75 (43)
		0.4204	0.5331	0.5410	0.3493
	Carcinoma, Hepatocellular	1/73 (42)	1/78 (45)	1/74 (33)	2/75 (43)
		0.2756	0.2646	0.6897	0.5089
	Hepatocellular_A+C	3/73 (42)	3/78 (45)	4/74 (33)	5/75 (43)
		0.1947	0.6944	0.3652	0.3698
	Osteosarcoma	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
		0.4658	NC	0.4400	NC
Lung	Adenocarcinoma	0/73 (42)	1/78 (44)	3/74 (35)	0/75 (42)
		0.5160	0.5116	0.0895	NC
	Adenoma, Bronchiolar	11/73 (44)	3/78 (46)	6/74 (36)	8/75 (44)
	Alveolar	0.5072	0.9844	0.7347	0.6974
	Carcinoma, Bronchiolar	5/73 (43)	6/78 (45)	4/74 (33)	2/75 (43)
	Alveolar	0.8883	0.5327	0.6096	0.7834
	Bronchiolar Alveolar_A+C	16/73 (45)	9/78 (47)	10/74 (36)	10/75 (45)
		0.8122	0.9779	0.8375	0.9487
	Carcinoma, Subcapsular Cell	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
	Osteosarcoma	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
		0.4658	NC	0.4400	NC
Lymph Node, Axillary	Adenocarcinoma	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
		0.4658	NC	0.4400	NC
Lymph Node, Mandibular	Fibrosarcoma	0/73 (42)	1/78 (45)	0/74 (33)	0/75 (42)
		0.4630	0.5172	NC	NC
Mammary Gland	Adenocarcinoma	0/73 (42)	3/78 (45)	6/74 (36)	1/75 (43)
		0.3959	0.1339	0.0076 **	0.5059
Multicentric Neoplasm	Hemangioma	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
		0.4658	NC	0.4400	NC
	Hemangiosarcoma	12/73 (46)	9/78 (48)	13/74 (39)	15/75 (45)
		0.1010	0.7276	0.3110	0.2992
	Leukemia, Granulocytic	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
		0.4658	NC	0.4400	NC
	Lymphoma	17/73 (48)	17/78 (51)	13/74 (39)	17/75 (49)
		0.4883	0.5028	0.4897	0.4452
	Mast Cell Tumor	0/73 (42)	1/78 (45)	0/74 (33)	0/75 (42)
		0.4630	0.5172	NC	NC
	Sarcoma, Histiocytic	1/73 (42)	4/78 (46)	1/74 (33)	4/75 (44)
		0.2149	0.2099	0.6897	0.1949
Ovaries	Adenoma, Tubulostromal	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
		0.4658	NC	0.4400	NC
	Carcinoma, Tubulostromal	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
	Cell	0.4658	NC	0.4400	NC
	Choriocarcinoma	0/73 (42)	1/78 (44)	0/74 (33)	0/75 (42)
		0.4658	0.5116	NC	NC

File Name: NDA211616Carcin

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - L vs. C	75 mg Mid (M) P - M vs. C	150 mg High (H) P - H vs. C
	Cystadenoma	5/73 (42)	1/78 (44)	1/74 (33)	3/75 (43)
		0.6120	0.9092	0.8345	0.6569
	Dysgerminoma	0/73 (42)	1/78 (44)	0/74 (33)	0/75 (42)
		0.4658	0.5116	NC	NC
	Sex-Cord/Stromal Tumor	2/73 (42)	1/78 (44)	1/74 (33)	2/75 (43)
		0.4474	0.5176	0.4092	0.3169
Pancreas	Adenoma, Islet Cell	0/73 (42)	0/78 (44)	0/74 (33)	2/75 (42)
		0.0668	NC	NC	0.2470
Pituitary Gland	Adenoma, Pars Distalis	4/73 (42)	3/78 (45)	2/74 (33)	1/75 (42)
		0.8940	0.5391	0.5410	0.8202
	Adenoma, Pars Intermedia	0/73 (42)	1/78 (45)	1/74 (33)	0/75 (42)
		0.4930	0.5172	0.4400	NC
	Carcinoma, Pars Distalis	0/73 (42)	1/78 (45)	0/74 (33)	0/75 (42)
		0.4630	0.5172	NC	NC
	Pars Distalis_A+C	4/73 (42)	4/78 (45)	2/74 (33)	1/75 (42)
		0.9391	0.6818	0.8345	0.9724
Skeletal Muscle, Diaphragm	Osteosarcoma	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
		0.4658	NC	0.4400	NC
Skin, Subcutis	Carcinoma, Squamous Cell	0/73 (42)	0/78 (44)	0/74 (33)	1/75 (42)
		0.2609	NC	NC	0.5000
	Fibrosarcoma	2/73 (42)	3/78 (46)	2/74 (33)	2/75 (43)
		0.5234	0.5436	0.5962	0.3169
	Sarcoma, Undifferentiated	0/73 (42)	0/78 (44)	0/74 (33)	1/75 (43)
		0.2654	NC	NC	0.5059
Stomach, Nonglandular	Sarcoma, Undifferentiated	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
Tail	Fibrosarcoma	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
		0.4658	NC	0.4400	NC
Thyroid Gland	Adenoma, Follicular Cell	0/73 (42)	1/78 (44)	0/74 (33)	1/75 (42)
		0.3179	0.5116	NC	0.5000
Tooth/Teeth	Fibroma, Odontogenic	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
Urinary Bladder	Carcinoma, Transitional Cell	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
Uterus With Cervix	Adenocarcinoma	2/73 (42)	0/78 (44)	0/74 (33)	1/75 (42)
		0.5879	0.7644	0.6897	0.5000
	Dysgerminoma	0/73 (42)	1/78 (44)	0/74 (33)	0/75 (42)
		0.4658	0.5116	NC	NC
	Fibroma	1/73 (42)	0/78 (44)	0/74 (33)	1/75 (42)
		0.4959	0.5116	0.4400	NC
	Fibrosarcoma	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
	Granular Cell Tumor	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
	Leiomyosarcoma	0/73 (42)	1/78 (45)	0/74 (33)	0/75 (42)

Reference ID: 4465565

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	25 mg Low (L) P - L vs. C	75 mg Mid (M) P - M vs. C	150 mg High (H) P - H vs. C
		0.4630	0.5172	NC	NC
	Polyp, Glandular	6/73 (45)	1/78 (45)	4/74 (35)	6/75 (43)
		0.2152	0.9449	0.4619	0.5882
	Polyp, Stromal	8/73 (43)	6/78 (46)	5/74 (35)	7/75 (44)
		0.5209	0.6660	0.5776	0.5197
	Sarcoma, Endometrial Stromal	1/73 (42)	0/78 (44)	0/74 (33)	0/75 (42)
		0.7391	0.5116	0.4400	0.5000
	Sarcoma, Stromal	2/73 (42)	2/78 (45)	0/74 (33)	2/75 (43)
		0.5028	0.3347	0.6897	0.3169
Whole Body	Hemangioma	0/73 (42)	0/78 (44)	1/74 (33)	0/75 (42)
		0.4658	NC	0.4400	NC
	Hemangiosarcoma	12/73 (46)	9/78 (48)	13/74 (39)	15/75 (45)
		0.1010	0.8647	0.3110	0.2992
	Hemangioma/	12/73 (46)	9/78 (48)	14/74 (39)	15/75 (45)
	Hemangiosarcoma	0.0955	0.8647	0.2289	0.2992

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Reference ID: 4465565

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

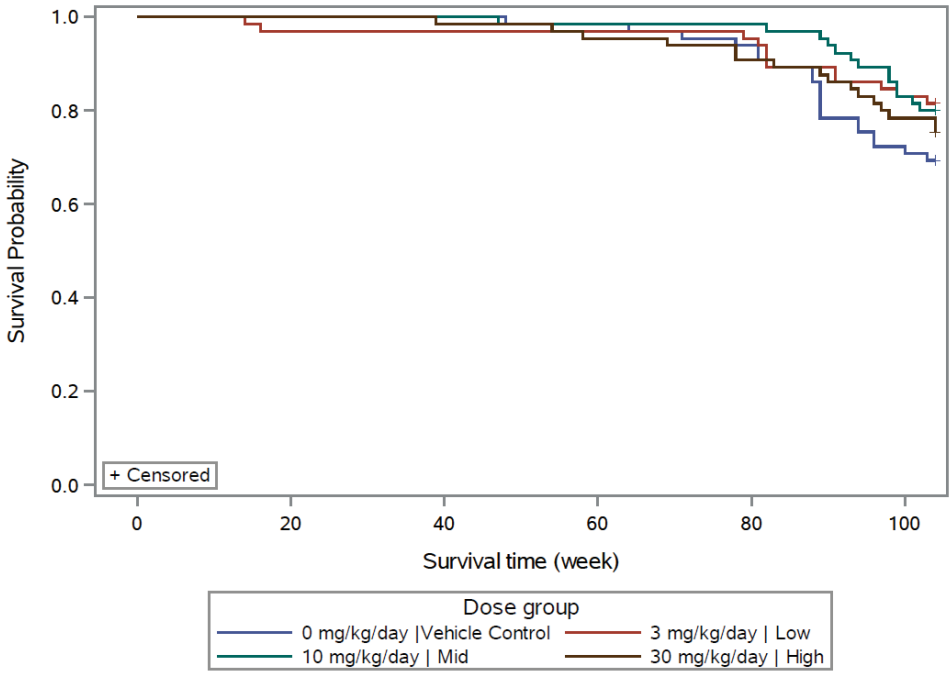

Figure 1B: Kaplan-Meier Survival Functions for Female Rats

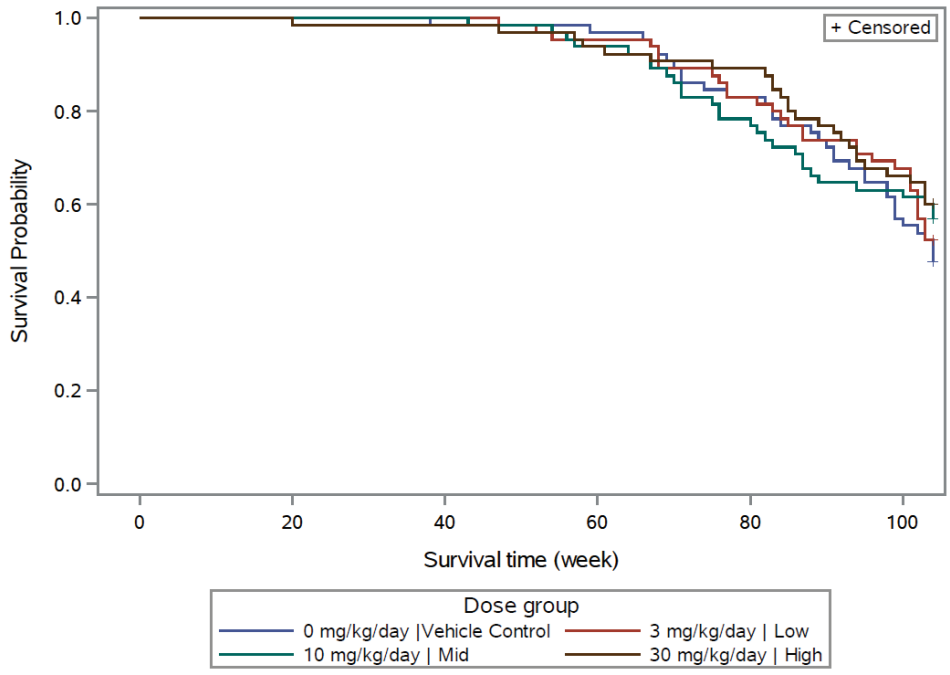

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Figure 2A: Kaplan-Meier Survival Functions for Male Mice

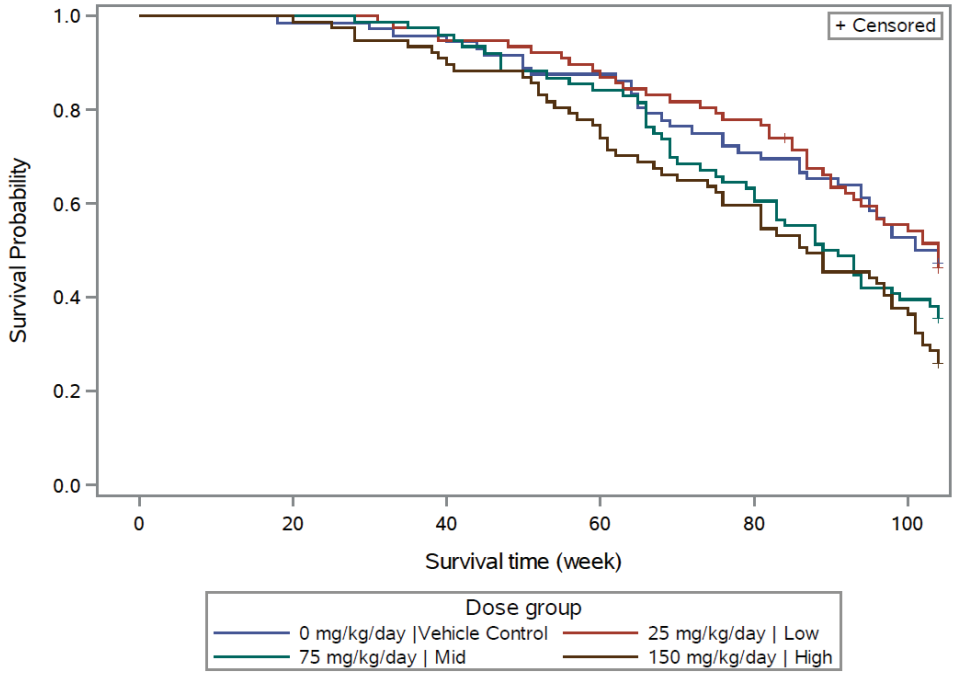
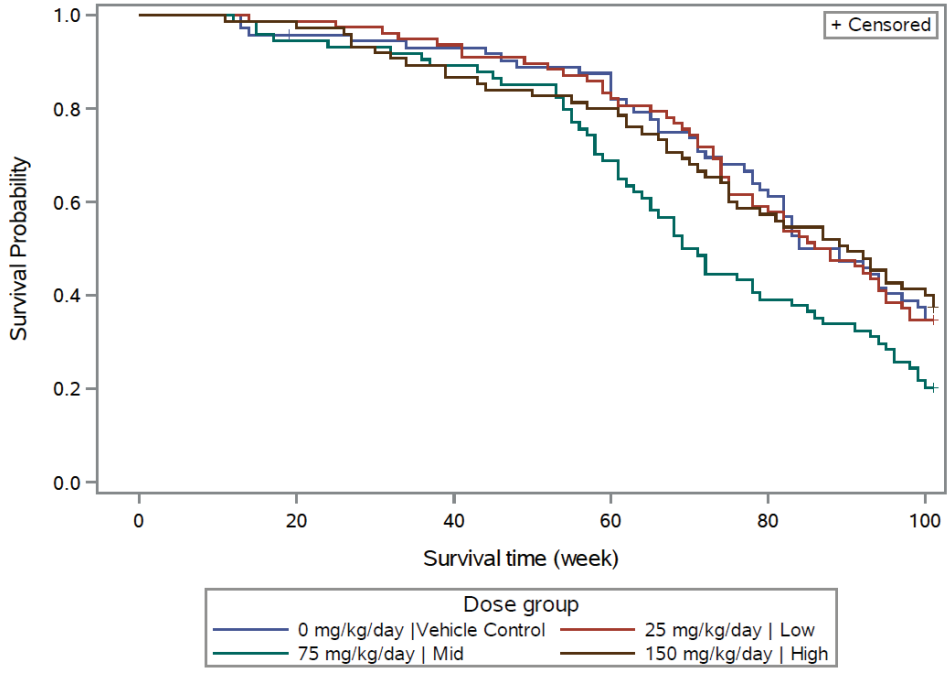


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



Reference ID: 4465565

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