ESPERION®

1002FDC-075

An Open-Label Postmarketing Milk-Only Lactation Study to Evaluate the Concentration of Bempedoic Acid and Bempedoic Acid and Ezetimibe in the Breast Milk of Healthy Lactating Women Administered Therapeutic Doses of Bempedoic Acid or Bempedoic Acid/Ezetimibe Fixed Combination Drug Product (FCDP)

Study Phase:	4
Indication:	Treatment of hyperlipidemia
Principal Investigator:	1 to 2 sites in the United States
Sponsor:	Esperion Therapeutics, Inc. 3891 Ranchero Drive, Suite 150 Ann Arbor, MI 48108 Phone: 1-734-887-3903 Fax: 1-734-913-5344
Sponsor Contact:	[redacted], MD, MPH, MSc Senior Vice President of Clinical Development and Pharmacovigilance

Version	Date
Amendment 1	06 June 2023
Final Protocol	18 August 2021

Confidentiality Statement

2. SYNOPSIS

Name of Sponsor: Esperion Therapeutics, Inc.

Name of Investigational Products: Bempedoic acid and bempedoic acid/ezetimibe fixed combination drug product (FCDP)

Name of Active Ingredients: bempedoic acid, ezetimibe

Title of Study: An Open-Label Postmarketing Milk-Only Lactation Study to Evaluate the Concentration of Bempedoic Acid and Bempedoic Acid and Ezetimibe in the Breast Milk of Healthy Lactating Women Administered Therapeutic Doses of Bempedoic Acid or Bempedoic Acid/Ezetimibe Fixed Combination Drug Product (FCDP)

Study Number: 1002FDC-075

Phase of Development: 4

Clinical Sites: 1 to 2 sites in United States

Objectives:

Primary:

The primary objectives of this study are to estimate infant exposure to bempedoic acid or bempedoic acid and ezetimibe:

- estimate the daily infant dosage and relative infant dose (RID) of bempedoic acid in mature breast milk after administration of bempedoic acid for 6 consecutive days, and
- estimate the daily infant dosage and RID of bempedoic acid and ezetimibe in mature breast milk after administration of bempedoic acid/ezetimibe FCDP for 6 consecutive days.

Secondary:

The secondary objectives of this study are to characterize the excretion of bempedoic acid or bempedoic acid and ezetimibe in mature breast milk of healthy lactating women who receive a once daily dose of bempedoic acid or bempedoic acid/ezetimibe FCDP for 6 consecutive days:

- determine concentrations of bempedoic acid, active metabolite ESP15228 and bempedoic acid glucuronide in mature breast milk collected over 24 hours from healthy subjects administered bempedoic acid or bempedoic acid/ezetimibe FCDP, and
- determine concentrations of ezetimibe and metabolite ezetimibe-glucuronide in mature breast milk collected over 24 hours from healthy subjects administered bempedoic acid/ezetimibe FCDP.

Safety:

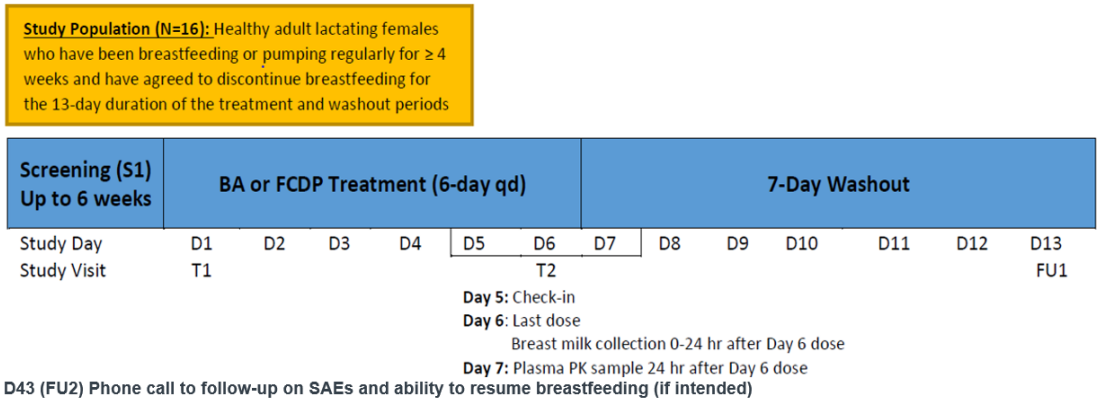
The safety objective of this study is to evaluate the safety of 6 consecutive doses of bempedoic acid or bempedoic acid/ezetimibe FCDP in healthy lactating women.

Study Design:

This is a Phase 4, open-label study that will estimate the daily infant dosage and RID of bempedoic acid and bempedoic acid/ezetimibe in the mature breast milk of healthy women who have received 6 daily doses of bempedoic acid or bempedoic acid/ezetimibe FCDP. The excretion of bempedoic acid, ezetimibe, and metabolites ESP15228, bempedoic acid glucuronide, and ezetimibe-glucuronide will be characterized in mature breast milk. Healthy lactating women who choose to stop breastfeeding their infant for the duration of the Treatment and Washout Periods will be eligible to participate once all

enrollment criteria are met. The Screening Period will be up to 42 days followed by a 6-day Treatment Period and a 7-day Washout Period. Subjects will be contacted by phone as a Post-treatment Follow-up Visit on Day 13. Once the call is complete, subjects may resume feeding their infant breast milk that is currently being produced.

Screening Period: The Screening Period will begin with a Screening Visit (Visit S1) that will occur up to 42 days prior to randomization (Visit T1). Visit S1 will allow the Investigator to assess the subject's eligibility and current breastfeeding practices. After the subject provides written informed consent, the subject will undergo screening assessments as outlined in Appendix 1. Study staff will schedule an optional lactation consultant visit for those subjects who desire support related to feeding/care of the infant such as preparing for the treatment and washout periods of the study, pumping breast milk for storage, introducing infant formula, introducing bottle feeding or resuming breastfeeding after Day 13 (FU1). Additional lactation consultant visits may be scheduled for subjects anytime throughout the study.



Treatment Period: Subjects who meet all eligibility criteria will be instructed to report to the clinical research unit (CRU) on Day 1 (Visit T1). Subjects who continue to meet eligibility criteria must confirm their infant is able to feed from a bottle, adequate stored breast milk and/or infant formula is available to feed the infant for the duration of the study, and the subject is maintaining adequate breast milk production. If a subject is weaning, duration of weaning will be documented. Subjects will then be randomized in a 1:1 ratio to receive either bempedoic acid (Cohort 1) or bempedoic acid/ezetimibe FCDP (Cohort 2). Eight subjects will be in each cohort. While at the CRU, subjects will provide a predose blood sample for pharmacokinetic (PK) and safety laboratories. Subjects will use an electric breast pump to provide a predose breast milk sample and will then receive the first dose of investigational medicinal product (IMP). When Visit T1 assessments are complete, subjects will be provided with adequate IMP supply to support once-daily dosing on Days 2, 3, 4 and 5 by self administration- at home. Subjects will be reminded that their infant(s) must not be fed with their breast milk that is produced after the first dose of IMP through Day 13 of the Washout Period. On Day 2 through Day 5 study staff will contact each subject by phone to ensure IMP is taken appropriately and remind the subject to discard breast milk that is produced after the first dose of IMP. In addition, subjects will document the day and time of when IMP was taken for Day 2 through Day 5 in the Study Drug Diary. On the evening of Day 5 (Visit T2), subjects will check-in to the CRU for 2 overnights (with Sponsor approval, subjects may check-in to the CRU on the morning of Day 6). Subjects must submit their Study Drug Diary at CRU check-in. Study staff will review the diary and assess IMP adherence. On the morning of Day 6, subjects will pump both breasts with an electric pump until completely emptied. When pumping is complete, Cohort 1 subjects will receive the Day 6 dose of bempedoic acid and Cohort 2 subjects will receive the Day 6 dose of bempedoic acid/ezetimibe FCDP. Breast milk will be collected from each subject over the next 24 hours using an electric pump at 3, 6, 9, 12, 16, 20 and 24 hours (±30 minutes) after Day 6 dose administration. Both breasts will be emptied completely during each collection. At each sampling time point, milk collected from each breast will be mixed together and the total volume measured and recorded. On Day

7, blood will be collected approximately 24 hours after Day 6 dosing for PK and safety laboratory samples. Subjects will be discharged from the CRU on the morning of Day 7 after breast milk collection and completion of Day 7 assessments. Subjects will be instructed to continue to pump and discard breast milk during the remainder of the Washout Period through Day 13. ***Follow-up Period:*** On Day 13, all subjects will be contacted by phone as a post-treatment Follow-up Visit (Visit FU1/End-of-Study [EOS]). Breastfeeding may resume after Visit FU1 on Day 13. An optional lactation consultant visit will be scheduled for those subjects who desire to re-establish breastfeeding. On Day 43 (FU2), study staff will contact subjects by phone to assess for SAEs and if the patient was able to resume breastfeeding (if intended).
Number of Subjects (planned): Approximately 16 (8 bempedoic acid [Cohort 1] and 8 bempedoic acid/ezetimibe FCDP [Cohort 2]) healthy lactating female subjects will be enrolled. If a subject discontinues the study early or does not receive 6 daily doses of IMP or does not complete the 24-hour breast milk collection after Day 6 dosing, a replacement subject will be enrolled and assigned to the same treatment.

Diagnosis and Criteria for Inclusion:

Inclusion Criteria:

Each subject must meet the following criteria to be eligible for this study.

1. The subject must be willing to provide written informed consent before any study-specific procedures are performed.
2. The subject must be 18 to 45 years old, inclusive.
3. The subject must be a lactating female who had a normal full-term pregnancy and has been actively breastfeeding or pumping for at least 4 weeks; lactation must be well -established per Investigator discretion.
4. The subject must be willing to pump regularly during the study to maintain milk supply and discontinue breastfeeding for the entire 13-day Treatment and Washout Periods.
5. The subject must not be pregnant.
6. The subject must be surgically sterile by hysterectomy, bilateral oophorectomy, and/or tubal ligation, or willing to use 1 acceptable method of birth control unless they have agreed to follow the definition of abstinence. The minimal requirement of adequate contraception should be started on Day 1 and continued during the study period and for at least 30 days after the last dose of IMP. Acceptable methods of birth control include:
   - an intrauterine device (IUD) with or without hormones;
   - established use of oral, implanted, transdermal, injectable, or hormonal method of contraception associated with inhibition of ovulation;
   - barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly;
   - vasectomized male partner who is the sole partner for this subject; or
   - true abstinence (when this is in line with the preferred and usual lifestyle of the subject). Note: periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods), declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception.

Exclusion Criteria:

Subjects who meet any of the following criteria will not be eligible to participate in this study.

1. Has clinically significant infection (e.g., pneumonia, pyelonephritis) or chronic infection within 30 days prior to enrollment.
2. Has evidence of unstable or uncontrolled, clinically significant cardiovascular, central nervous system, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder, including serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash, that, in the opinion of the Investigator, would confound the study results or compromise subject safety.
3. Has estimated glomerular filtration rate (eGFR) <30 mL/min/1.73^2 using the Modification of Diet in Renal Disease (MDRD) formula.
4. Has liver disease or dysfunction characterized by Child-Pugh Class B or Class C.
5. History of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
6. Has active psychiatric problems that, in the Investigator's opinion, may interfere with compliance with the study procedures.
7. Is unable to participate in all the study visits or comply with study procedures.
8. Has history of breast implants, breast augmentation, or breast reduction surgery.
9. Has a prior history of difficulty establishing lactation.
10. Gastrointestinal conditions or procedures (including weight loss surgery; e.g., Lap-Band® or gastric bypass) that may affect drug absorption.
11. Any history of malignancy (with the exception *only* of basal or squamous cell carcinoma of the skin

in individuals that have been cancer free for >5 years).
12. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Subjects with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
13. Current smoker.
14. Blood donation, participation in a multiple blood draw clinical study, major trauma, or surgery with or without blood loss within 30 days prior to enrollment.
15. Blood transfusion for any reason within 90 days prior to enrollment.
16. Use of any 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor (statin) concurrently or within 30 days prior to randomization (Visit T1).
17. Use of cyclosporine, cholestyramine, probenecid, fibrate drugs, or medications contraindicated during lactation concurrently or within 30 days prior to randomization (Visit T1).
18. Concomitant use or use within 30 days prior to randomization (Visit T1) of drugs that decrease breast milk production, such as pseudoephedrine.
19. Concomitant use or use within 30 days prior to randomization (Visit T1) of drugs that increase breast milk production, such as domperidone.
20. Use of any experimental or investigational drugs/vaccines concurrently or within 30 days or 5 half-lives of the drug, whichever is longer, prior to screening (Visit S1).
21. Any current condition that in either the Investigator's, Sponsor's, or authorized Medical Monitor's opinion may compromise subject safety or ability to complete the study or interfere with study data interpretation.
22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.

Investigational Medicinal Product(s) (IMPs), Dose, and Mode of Administration:

Bempedoic acid 180 mg or bempedoic acid 180 mg/ezetimibe 10 mg FCDP will be administered orally once daily for 6 days.

Duration of Study:

The expected study duration for all subjects is ≤55 days, including an up to 42-day Screening Period, followed by a 6-day Treatment Period, and a 7-day Washout Period.

Pharmacokinetic Assessments

Primary Endpoints

Bempedoic acid and ezetimibe assessments:

- Daily infant dosage calculated as the cumulative amount excreted in breast milk per day
- RID calculated as the ratio of total infant daily dose per kg of body weight and maternal daily dose per kg of body weight multiplied by 100

Secondary Endpoints

Bempedoic acid, ezetimibe, and metabolite (ESP15228, bempedoic acid glucuronide, and ezetimibe-glucuronide) assessments:

- Amount excreted in each breast milk collection, calculated as the product of concentration and milk volume collected
- Area under the milk concentration-time curve (AUC) over the 24-hour collection interval
- Average milk concentration based on milk AUC
- Peak and trough milk concentrations and the time of peak milk concentrations
- Plasma trough concentrations at 24 hours after the last dose on Day 6

Safety Assessments:

Adverse events (all and treatment emergent), clinical laboratory parameters, vital signs, and physical examinations.

Statistical Methods:

A minimum sample size of 16 (8 bempedoic acid [Cohort 1] and 8 bempedoic acid/ezetimibe FCDP [Cohort 2]) evaluable subjects (who complete the 6-day treatment period and 24-hour breast milk collection) is planned for this study. The sample size was determined to be sufficient to address the objectives of the study. Sample size was not based on empirical or hypothesis testing criteria

Breast milk PK endpoints of daily infant dosage, RID, amount excreted, AUC and peak, trough and average concentrations will be summarized using descriptive statistics for bempedoic acid, ESP15228, bempedoic acid glucuronide, ezetimibe and ezetimibe glucuronide. Plasma trough concentrations of bempedoic acid, ESP15228, bempedoic acid glucuronide, ezetimibe and ezetimibe glucuronide will be summarized using descriptive statistics.

For all enrolled subjects who receive at least 1 dose of IMP (safety population), safety data (including adverse events, clinical laboratory parameters, physical examination, vital signs and body weight) will be summarized and listed using descriptive statistics.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
ACL	adenosine triphosphate-citrate lyase
ACS	acyl-CoA synthetase
ACSVL1	very long-chain acyl-CoA synthetase 1
ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ApoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the concentration time curve
AUC_{0-24}	area under the concentration time curve from 0 to 24 hours
BA	bempedoic acid
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
CK	creatine kinase
CPK	creatine phosphokinase
Cl	chloride
CNS	central nervous system
CoA	acetyl-coenzyme A
CO_2	carbon dioxide
CRO	contract research organization

Abbreviation or Specialist Term	Explanation
CVD	cardiovascular disease
CYP	cytochrome P450
DBP	diastolic blood pressure
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EZE	ezetimibe
FCDP	fixed combination drug product
FCMP	fixed combination medicinal product
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
Hct	hematocrit
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
Hgb	hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	intrauterine device
K	potassium
LDL-C	low-density lipoprotein cholesterol
LSM	least squares mean
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MED ID	medication identification
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialist Term	Explanation
MI	myocardial infarction
N/A	not applicable
N/D	not done
NOAEL	no-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein cholesterol
PCSK9	proprotein convertase subtilisin kexin type 9
PE	physical exam
PK	pharmacokinetic(s)
RBC	red blood cell
RID	relevant infant dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP(s)	standard operating procedure(s)
SP	Safety Population
SUSAR	suspected and unexpected serious adverse reaction
TB	total bilirubin
TC	total cholesterol
TEAE(s)	treatment-emergent adverse event(s)
TMF	Trial Master File
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	white blood cell
WHO	World Health Organization

4. INTRODUCTION

Bempedoic acid (ETC-1002) is an oral, first-in class, small molecule that inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Bempedoic acid, like statins, up-regulates low density lipoprotein cholesterol (LDL-C) receptors.

Bempedoic acid 180 mg and bempedoic acid 180 mg/ezetimibe 10 mg fixed combination drug product (FCDP), under the marketed names of Nexletol® and Nexlizet®, respectively, have been approved by the United States (US) Food and Drug Administration (FDA) as an adjunct to diet and maximally tolerated statin therapy for the treatment of heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease in adults who require additional lowering of LDL-C (Nexletol 2020 USPI; Nexlizet 2020 USPI). In the European Union (EU) bempedoic acid and bempedoic acid/ezetimibe fixed combination medicinal product (FCMP) have been approved by the European Commission and are marketed under the names Nilemdo® and Nustendi®, respectively, for the treatment of primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in adults unable to reach LDL-C goals with the maximum tolerated dose of statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated. Additionally, Nustendi is indicated in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin (Nilemdo 2020 SmPC; Nustendi 2020 SmPC).

Bempedoic acid and bempedoic acid/ezetimibe FCDP have been studied in adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional LDL-C lowering but data do not exist for lactating women who may choose to continue breastfeeding their infant in conjunction with bempedoic acid or bempedoic acid/ezetimibe FCDP therapy. There is no information regarding the excretion of bempedoic acid in human or animal milk, the effects of bempedoic acid on the breastfed infant, or the effects of bempedoic acid on milk production. Bempedoic acid decreases cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and theoretically may cause harm to the breastfed infant. In addition, it is not known whether ezetimibe is excreted into human milk. In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma (Zetia 2020 USPI).

The USPIs for bempedoic acid (Nexletol 2020 USPI) and bempedoic acid/ezetimibe FCDP (Nexlizet 2020 USPI) note breastfeeding is not recommended with either therapy and the SmPCs for bempedoic acid (Nilemdo 2020 SmPC) and bempedoic acid/ezetimibe FCMP (Nustendi 2020 SmPC) state breastfeeding is contraindicated. As a result of the current labeling in conjunction with the paucity of data, patients, along with their health care providers, must make decisions about bempedoic acid and bempedoic acid/ezetimibe FCDP therapy during lactation with a lack of evidence-based data regarding the excretion of bempedoic acid or bempedoic acid and ezetimibe into breast milk and the potential exposure to the breast fed infant.

4.1 Study Rationale

This Phase 4 study is designed to characterize the excretion of bempedoic acid or bempedoic acid and ezetimibe into mature breast milk of healthy lactating women and assess the exposure to the breast fed infant by estimating the daily infant dosage and the relative infant dose (RID) of bempedoic acid or bempedoic acid and ezetimibe in breast milk after 6 consecutive daily doses of bempedoic acid or bempedoic acid/ezetimibe FCDP.

4.2 Background of Bempedoic Acid and Bempedoic Acid/Ezetimibe FCDP

Bempedoic acid is an ACL inhibitor that lowers LDL-C by inhibition of cholesterol synthesis in the liver. Adenosine triphosphate-citrate lyase is an enzyme upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. 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 ESP 15228-CoA, respectively. Inhibition of ACL by ETC-1002-CoA results in decreased cholesterol synthesis in the liver and lowers LDL-C in blood via upregulation of low-density lipoprotein receptors.

Bempedoic acid and bempedoic acid/ezetimibe FCDP have been approved by the FDA and European Medicines Agency (EMA) based on the positive safety and efficacy profiles of large Phase 3 programs that evaluated adults with primary and secondary hyperlipidemia who required additional LDL-C lowering. Please refer to the most recent Investigator Brochure (IB) for more detailed information regarding nonclinical experience and previous human experience along with the USPIs and the SmPCs for bempedoic acid and bempedoic acid/ezetimibe FCDP.

4.3 Dose Selection

A dose of bempedoic acid 180 mg once per day was selected based on approved doses by the US FDA (Nexletol) and the European Medicines Agency (Nilemdo). The dose for bempedoic acid/ezetimibe FCDP (bempedoic acid 180 mg/ezetimibe 10 mg) was selected based on approved doses by the US FDA (Nexlizet) and the European Medicines Agency (Nustendi). For additional information please refer to the most recent IB, the USPIs for Nexletol and Nexlizet and the SmPCs for Nilemdo and Nustendi.

Subjects enrolled in the study will be dosed for 6 consecutive days in order to reach steady-state concentrations of bempedoic acid or bempedoic acid and ezetimibe in plasma. Steady-state concentrations in plasma are expected after 5 to 7 days of repeat dosing as estimates of elimination half-life of bempedoic acid and ezetimibe are each approximately 24 hours. A once daily dosing regimen for 6 days will achieve plasma concentrations that are approximately 98% of steady-state levels. Six days of repeat dosing have been selected to ensure subjects are at steady-state plasma concentrations of bempedoic acid or bempedoic acid and ezetimibe for pharmacokinetic (PK) assessments.

4.4 Risk Benefit Summary

Subjects in this clinical study are healthy lactating volunteers who choose to stop breastfeeding their infant for the duration of the Treatment and Washout Periods (13 days) and will not receive any health benefit from participating in this study. Both bempedoic acid and bempedoic acid/ezetimibe FCDP are approved by the FDA and EMA.

This study will provide evidence-based data to inform lactating women in the US with HeFH or ASCVD and their health care providers whether to continue with treatment of bempedoic acid or bempedoic acid/ezetimibe FCDP during breast feeding.

Please refer to the most recent IB for more detailed information regarding previous human experience along with the USPIs and the SmPCs for bempedoic acid and bempedoic acid/ezetimibe FCDP.

5. OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objectives of this study are to estimate infant exposure to bempedoic acid or bempedoic acid and ezetimibe:

- estimate the daily infant dosage and the relative infant dose (RID) of bempedoic acid in mature breast milk after administration of bempedoic acid for 6 consecutive days, and
- estimate the daily infant dosage and RID of bempedoic acid and ezetimibe in mature breast milk after administration of bempedoic acid/ezetimibe FCDP for 6 consecutive days.

5.1.2 Secondary Objectives

The secondary objectives of this study are to characterize the excretion of bempedoic acid or ezetimibe in mature breast milk of healthy lactating women who receive once daily dose of bempedoic acid or bempedoic acid/ezetimibe FCDP for 6 consecutive days:

- determine concentrations of bempedoic acid, active metabolite ESP15228 and bempedoic acid glucuronide in mature breast milk collected over 24 hours from healthy subjects administered bempedoic acid or bempedoic acid/ezetimibe FCDP, and
- determine concentrations of ezetimibe and metabolite ezetimibe-glucuronide in mature breast milk collected over 24 hours from healthy subjects administered bempedoic acid/ezetimibe FCDP.

5.1.3 Safety Objective

The safety objective of this study is to evaluate the safety of 6 consecutive doses of bempedoic acid or bempedoic acid/ezetimibe FCDP in healthy lactating women.

5.2 Endpoints

5.2.1 Pharmacokinetic Assessments

5.2.1.1 Primary Endpoints

Bempedoic acid and ezetimibe assessments include:

- daily infant dosage calculated as the cumulative amount excreted in breast milk per day, and
- RID calculated as the ratio of total infant daily dose per kg body weight and maternal daily dose per kg of body weight multiplied by 100.

5.2.1.2 Secondary Endpoints

Bempedoic acid, ezetimibe, and metabolites (ESP15228, bempedoic acid glucuronide, and ezetimibe-glucuronide) assessments include:

- amount excreted in each breast milk collection, calculated as the product of concentration and milk volume collected,
- area under the milk concentration-time curve (AUC) over the 24-hour collection interval,
- average milk concentration based on milk AUC,
- peak and trough milk concentrations and the time of peak milk concentrations, and
- plasma trough concentrations at 24 hours after the last dose on Day 6.

5.2.2 Safety Endpoints

Adverse events (all and treatment-emergent), clinical laboratory parameters, vital signs, and physical examinations will be collected.

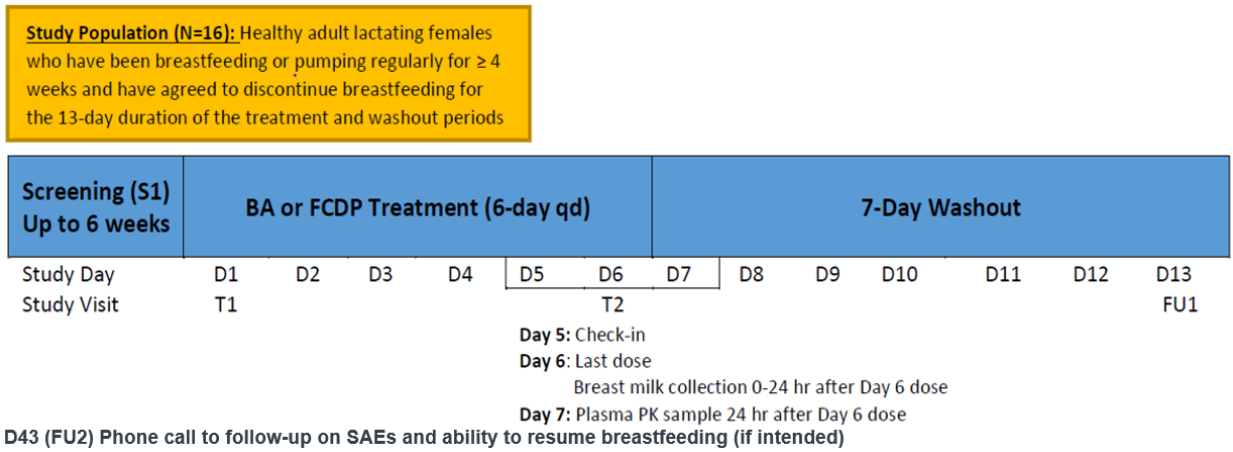
6. INVESTIVATIONAL PLAN

6.1 Overall Study Design

This is a Phase 4, open-label study that will estimate the daily infant dosage and RID for bempedoic acid and bempedoic acid/ezetimibe FCDP and characterize the excretion of bempedoic acid, ezetimibe, and metabolites ESP 15228, bempedoic acid glucuronide, and ezetimibe-glucuronide in the mature breast milk of healthy women. The study will enroll 16 healthy lactating subjects, who will be randomized in a 1:1 ratio to receive either bempedoic acid (Cohort 1) or bempedoic acid/ezetimibe FCDP (Cohort 2), who choose to stop breastfeeding their infant for the duration of the Treatment and Washout periods (13 days). After signing the informed consent form (ICF), subjects will enter the Screening Period for up to 42 days, followed by a 6-day Treatment Period and a 7-day Washout Period. At Visit T1, subjects will be administered IMP at the clinical research unit CRU. The IMP will then be self-administered at home on Day 2 through Day 5. Study staff will phone subjects Day 2 through Day 5 to ensure IMP is being taken appropriately and remind subjects to discard breast milk produced after the first dose of IMP. Subjects will check-in to the CRU on the evening of Day 5 (with Sponsor approval the subject may check-in to the CRU on the morning of Day 6) for Visit T2 and start a 24-hour breast milk collection after the last dose of IMP on the morning of Day 6. Serum PK samples will be obtained on Day 7, approximately 24 hours after IMP administration on Day 6. Subjects will be discharged from the CRU on the morning of Day 7 approximately 24 hours after Day 6 dosing and the completion of all Day 7 assessments. At the end of the Washout Period on Day 13, all subjects will be contacted by phone for a Post-treatment Follow-up Visit (Visit FU1). Once the call is complete, subjects may resume feeding their infants breast milk that is currently being produced. On Day 43 (Visit FU2), study staff will contact subjects by phone to assess for SAEs and if the patient was able to resume breastfeeding (if intended).

Please refer to Appendix 1 for a detailed Schedule of Assessments.

Figure 1: Study Schematic



6.2 Scientific Rationale

Consistent with the FDA's Draft Guidance for Industry, Clinical Lactation Studies: Considerations for Study Design (FDA May 2019) this Phase 4 study is designed to characterize the excretion of bempedoic acid or bempedoic acid and ezetimibe in mature human breast milk.

The data generated from this study will aid in assessing exposure and potential effects on the breastfed infant.

6.3 Estimated Study Duration

Each subject will be in the study for up to 55 days. The 55 days are inclusive of an up to 42 days Screening Period followed by a 6-day Treatment Period and a 7-day Washout Period.

6.4 Number of Centers

Up to 2 clinical research units (CRU) will participate in this study in the US. Additional sites may be invited to participate to ensure study timelines are met.

6.5 Number of Subjects

The study will enroll approximately 16 healthy lactating women randomized in a 1:1 ratio of bempedoic acid (Cohort 1) to bempedoic acid/ezetimibe FCDP (Cohort 2).

6.6 Subject Number and Identification

A unique subject identification number will be assigned to each subject to identify each subject throughout the study. Subject identification numbers will be assigned sequentially by the study site at the time of informed consent at the Screening Visit (Visit S1).

6.7 Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. Approximately 16 (8 bempedoic acid [Cohort 1] and 8 bempedoic acid/ezetimibe FCDP [Cohort 2]) healthy lactating female subjects will be enrolled. If a subject discontinues the study early or does not receive 6 daily doses of IMP or does not complete the 24-hour breast milk collection after Day 6 dosing, a replacement subject will be enrolled and assigned to the same treatment. The site must notify the Sponsor of any early withdrawals.

6.8 End of Study

A subject is considered to have completed the study if all phases of the study are completed including the Follow-up Visit (FU1) on Day 13.

The end of the study is defined as the date of the Follow-up Visit (FU1) on Day 13 for the last active subject in the study.

Study staff will contact subjects by phone 30 days (Day 43, FU2) after FU1 to assess for serious adverse events (SAEs) and if the patient was able to resume breastfeeding (if intended).

7. SELECTION OF SUBJECTS

7.1 Subject Inclusion Criteria

Each subject must meet the following criteria to be eligible for this study.

1. The subject must be willing to provide written informed consent before any study-specific procedures are performed.
2. The subject must be 18 to 45 years old, inclusive.
3. The subject must be a lactating female who had a normal full-term pregnancy and has been actively breastfeeding or pumping for at least 4 weeks; lactation must be well-established per Investigator discretion.
4. The subject must be willing to pump regularly during the study to maintain milk supply and discontinue breastfeeding for the entire 13-day Treatment and Washout Periods.
5. The subject must not be pregnant.
6. The subject must be surgically sterile by hysterectomy, bilateral oophorectomy, and/or tubal ligation, or willing to use 1 acceptable method of birth control unless they have agreed to follow the definition of abstinence. The minimal requirement of adequate contraception should be started on Day 1 and continued during the study period and for at least 30 days after the last dose of IMP. Acceptable methods of birth control include:
   - an intrauterine device (IUD) with or without hormones;
   - established use of oral, implanted, transdermal, injectable, or hormonal method of contraception associated with inhibition of ovulation;
   - barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly;
   - vasectomized male partner who is the sole partner for this subject; or,
   - true abstinence (when this is in line with the preferred and usual lifestyle of the subject). Note: periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception.

7.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in this study.

1. Has clinically significant infection (e.g., pneumonia, pyelonephritis) or chronic infection within 30 days prior to enrollment.
2. Has evidence of unstable or uncontrolled, clinically significant cardiovascular, central nervous system, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder, including serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash, that, in the opinion of the Investigator, would confound the study results or compromise subject safety.

3. Has estimated glomerular filtration rate (eGFR) <30 mL/min/1.73^2 using the Modification of Diet in Renal Disease [MDRD] formula.
4. Has liver disease or dysfunction characterized by Child-Pugh Class B or Class C.
5. History of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
6. Has active psychiatric problems that, in the Investigator's opinion, may interfere with compliance with the study procedures.
7. Is unable to participate in all the study visits or comply with study procedures.
8. Has history of breast implants, breast augmentation, or breast reduction surgery.
9. Has a prior history of difficulty establishing lactation.
10. Gastrointestinal conditions or procedures (including weight loss surgery; e.g., Lap-Band® or gastric bypass) that may affect drug absorption.
11. Any history of malignancy (with the exception only of basal or squamous cell carcinoma of the skin in individuals that have been cancer free for >5 years).
12. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Subjects with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
13. Current smoker.
14. Blood donation, participation in a multiple blood draw clinical study, major trauma, or surgery with or without blood loss within 30 days prior to enrollment.
15. Blood transfusion for any reason within 90 days prior to enrollment.
16. Use of any HMG Co-A reductase inhibitor (statin) concurrently or within 30 days prior to enrollment.
17. Use of cyclosporine, cholestyramine, probenecid, fibrate drugs, or medications contraindicated during lactation concomitantly or within 30 days prior to randomization (Visit T1).
18. Concomitant use or use within 30 days prior to randomization (Visit T1) of drugs that decrease breast milk production, such as pseudoephedrine
19. Concomitant use or use within 30 days prior to randomization (Visit T1) of drugs that increase breast milk production, such as domperidone.
20. Use of any experimental or investigational drugs/vaccines concurrently or within 30 days or 5 half-lives of the drug, whichever is longer, prior to screening (Visit S1).
21. Any current condition that in either the Investigator's, Sponsor's, or authorized Medical Monitor's opinion may compromise subject safety or ability to complete the study or interfere with study data interpretation.
22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.

7.3 Screen Failures

Subjects who sign the ICF and enter the screening period of the study but do not meet all eligibility criteria at the time of randomization (Visit T1) will be considered a screen failure and will not be randomized into the study.

8. TREATMENT OF SUBJECTS

8.1 Administration of Investigational Medicinal Product

On Day 1 (Visit T1) of the Treatment Period, subjects will be randomized to receive bempedoic acid (Cohort 1) or bempedoic acid/ezetimibe FCDP (Cohort 2). Each dose of IMP is comprised of 1 tablet from a bottle. The CRU staff will administer IMP to subjects in the unit on Day 1 and Day 6 of the study. The IMP will be self-administered by subjects on Day 2 through Day 5 at home. Subjects will be instructed to take IMP once daily at approximately the same time each morning (± 2 hours) with or without food. On the evening of Day 5 (Visit T2), subjects will check-in to the CRU and CRU staff will administer IMP on the morning of Day 6.

Study staff will call subjects on Days 2 through Day 5 to ensure they are taking IMP appropriately. Day and time of IMP administration must be captured in the Study Drug Diary. If the subject forgets to take IMP at the same time (± 2 hours) Day 2 through Day 5, it may be taken up to 6 hours later the same day. After that, the subject should not take IMP that day and the Sponsor should be contacted to determine if the subject should continue or be replaced in the study. The details describing the reason for the missed dose should be documented in the subject's medical record. Extra IMP is provided and can be used to replace a dose of IMP that cannot be used if lost or damaged.

Other details regarding IMP including description, supply and control, accountability, handling, and disposal are provided in Section 0.

8.2 Prior and Concomitant Medications

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- reason for use,
- dates of administration including start and end dates, and
- dosage information including dose and frequency.

Subjects will be permitted to take concomitant medications except those listed in Section 8.2.1.

8.2.1 Prohibited Medications

Subjects may not use medications listed below within the time periods indicated and may not use the following drugs during the study:

- HMG Co-A reductase inhibitor (statin) concurrently or within 30 days prior to randomization (Visit T1);
- cyclosporine, cholestyramine, probenecid, fibrate drugs, or medications contraindicated during lactation concurrently or within 30 days prior to randomization (Visit T1);
- experimental or investigational drugs concurrently or within 30 days or 5 half-lives of the drug, whichever is longer, prior to screening (Visit S1);

- concomitant use or use within 30 days prior to randomization (Visit T1) of drugs that decrease breast milk production, such as pseudoephedrine; or
- concomitant use or use within 30 days prior to randomization (Visit T1) of drugs that increase breast milk production, such as domperidone.

8.2.2 Permitted Medications

Concomitant use of prescription or nonprescription medications, vaccines and supplements not listed in Section 8.2.1 are allowed during the study, upon prior consent of the Investigator (or designee) and Sponsor.

8.3 Concomitant Procedures

Any procedure that the subject undergoes after signing the ICF throughout the duration of the study must be recorded in the eCRF along with:

- date of the procedure, and
- reason for the procedure

8.4 Treatment Assignment, Randomization, and Blinding

8.4.1 Treatment Assignment

Subjects will receive open-label IMP during the Treatment Period of the study. Subjects will be randomized (Visit T1) to receive either bempedoic acid (Cohort 1) or bempedoic acid/ezetimibe FCDP (Cohort 2). The IMP will be taken Day 1 through Day 6 of the treatment period.

8.4.2 Randomization

Subjects will be randomized in a 1:1 ratio to receive either bempedoic acid (Cohort 1) or bempedoic acid/ezetimibe FCDP (Cohort 2) on Day 1 (Visit T1) of the treatment period. When the target number of subjects (8 in each cohort) is reached and all subjects have completed the 24-hour breast milk collection at the CRU, randomization will be closed. If a subject is randomized but did not complete the 24-hour breast milk collection in the CRU, she will be replaced with a new subject on the same treatment to ensure each cohort of the study has 8 evaluable subjects.

8.4.3 Blinding

This is an open-label study.

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1 Description of Investigational Medicinal Product

The IMP used for this study are described in Table 1. Please see the Pharmacy Manual for detailed storage requirements and instructions.

Table 1: Investigational Medicinal Products

	Investigational Medicinal Product	
Product Name:	**Bempedoic acid**	**Bempedoic acid/ezetimibe FCDP**
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	180 mg/10 mg
Container/Closure:	Bottle	Bottle
Route of Administration:	Oral, daily at similar time with or without food	Oral, daily at similar time with or without food
Physical Description:	Oval, white to off-white tablet debossed with "180" on one side and "ESP" on the other	Oval, blue tablet debossed with "818" on one side and "ESP" on the other

FCDP = Fixed combination drug product

9.2 Investigational Medicinal Product Supply and Control

The Sponsor will supply the IMPs for this study. The IMPs for this study, bempedoic acid and bempedoic acid/ezetimibe FCDP, have been approved by the FDA as Nexletol® and Nexlizet®, respectively. Investigational medicinal product will be distributed and released in accordance with regional and local requirements during the conduct of the study.

Investigational medicinal product will be dispensed by the Investigator or other qualified study personnel only to subjects who have provided informed consent.

9.3 Packaging and Labeling

Open-label IMP will be packaged in a bottle containing 30 tablets. The IMP labels will be compliant with the Code of Federal Regulations (CFR) Title 21 Section 312.6 Labeling of an Investigational New Drug.

9.4 Investigational Medicinal Product Adherence

On Day 2 through Day 5 subjects will document day and time IMP is taken in the Study Drug Diary and the diary will be submitted to study staff at check-in to the CRU on the evening of Day 5 (Visit T2). In addition, study staff will phone subjects on Day 2 through Day 5 to ensure subjects are taking IMP appropriately. Study staff will assess subject adherence through phone calls, review of the Study Drug Diary, and by counting the number of tablets returned at check-in to the CRU on the evening of Day 5. If a subject has missed a dose of IMP, the Sponsor will be notified immediately to determine if the subject should continue in the study or be replaced.

9.5 Investigational Medicinal Product Accountability

Subjects will be instructed to return all packaging and unused IMP at check-in to the CRU on Day 5 (Visit T2) for assessment of adherence and drug accountability.

Accurate records of the receipt of all IMP shipped by the Sponsor (or designee) and the disposition of that IMP must be maintained.

All IMP records or logs must comply with applicable regulations, local law, and guidelines, and should include the:

- amount received/placed in storage area;
- amount currently in storage area;
- MED ID/Kit number for all IMP;
- dates and initials of person(s) responsible for IMP inventory (including entry/movement/disposition);
- date and amount of IMP dispensed to each subject, including unique subject identifiers;
- date that IMP was returned by subject, assessment of adherence, and relevant documentation of discrepancies;
- nonstudy disposition (e.g., lost, broken, wasted); and
- amount returned to Sponsor (or designee)/destroyed or amount destroyed per local standard operating procedure (SOP) following accountability by site monitor.

9.6 Investigational Medicinal Product Handling, Storage, and Disposal

The Principal Investigator will ensure that all IMP is stored in a secure area, under recommended storage conditions. Bempedoic acid and bempedoic acid/ezetimibe FCDP must be stored at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C). Bempedoic acid must be stored and dispensed in the original package. Bempedoic acid/ezetimibe must be stored and dispensed in the original package protected from extreme heat and humidity. Access to IMP will be limited to those clinical site personnel authorized by the Investigator. Upon completion or termination of the study, all IMP and used and unused IMP packaging must be returned to the Sponsor (or designee) for eventual destruction unless otherwise authorized by the Sponsor. All IMP returns must be accompanied by the appropriate documentation.

10. STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

10.1 Informed Consent

The subject must be adequately informed of the nature and risks of the study and understand the ICF. It is the Investigator's responsibility that no study-related procedure will be performed until the subject has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an ICF approved by the Sponsor (or designee) and the Institutional Review Board (IRB). The written ICF should be prepared in the local language(s) of the potential subject population.

10.2 Electronic Case Report Forms (eCRFs)

Data will be captured on eCRFs.

10.3 Procedures and Schedule of Assessments

The study is comprised of 3 distinct periods: Screening Period, Treatment Period, and Washout/Follow-up Period.

The Schedule of Assessments is provided in Appendix 1; however, a subject can be seen at any time for reasons of safety.

Lactation consultant visits will be scheduled anytime during the study for those subjects who desire support related to feeding/care of the infant such as preparing for the treatment and washout periods of the study, pumping breast milk for storage, introducing infant formula, introducing bottle feeding or resuming breastfeeding after Day 13 (FU1).

If the subject discontinues IMP or misses a dose, please contact the Sponsor immediately to determine if subject should continue in the study or be replaced.

10.3.1 Screening Week -6 (Visit S1; Day -42 through Day -1)

The screening period will begin with a screening visit (Visit S1) that will occur up to 6 weeks prior to randomization (Visit T1). Visit S1 will allow the Investigator to assess the subject's eligibility. After the subject provides informed consent (Section 10.1), the subject will undergo the following assessments:

- demographics;
- medical history including gestational age of infant at delivery, date of delivery, stage of lactation, length of time post-partum, smoking and alcohol intake;
- Review of current breastfeeding practices per subject report, including:
  - frequency and duration of feeds for infants fed from the breast,
  - bottles/day and ounces/day for infant's fed pumped breast milk from a bottle, and
  - use of formula supplementation (bottles/day, ounces/day and duration of supplementation);
- confirm subject is maintaining adequate breast milk production (document duration of weaning, if applicable) per subject report;

- confirm infant is able to bottle feed prior to randomization (Visit T1) per subject report;
- confirm adequate breast milk/infant formula is available to feed the infant after first dose of IMP (Visit T1) through Day 13 (Visit FU1) per subject report;
- concomitant medication review;
- adverse event review;
- physical exam;
- weight, height, and BMI;
- vital signs;
- clinical lab evaluations (blood chemistry, hematology and serology);
- assessment of renal function (eGFR calculated according to MDRD formula);
- assessment for liver disease (according to Child Pugh Classification score);
- serum pregnancy test;
- urine drug and alcohol screen; and
- schedule optional lactation consultant visit.

Note: subjects must understand that they will not be able to feed their infant breast milk produced after the first dose of IMP through Day 13.

10.3.2 Treatment Day 1 (Visit T1)

Subjects who continue to meet all inclusion criteria and none of the exclusion criteria may be randomized into the study. Each subject will undergo the following assessments:

- Review of current breastfeeding practices per subject report, including:
  - frequency and duration of feeds for infants fed from the breast,
  - bottles/day and ounces/day for infant's fed pumped breast milk from a bottle, and
  - use of formula supplementation (bottles/day, ounces/day and duration of supplementation);
- confirm subject is maintaining adequate breast milk production (document duration of weaning, if applicable) per subject report;
- confirm infant is able to bottle feed prior to randomization (Visit T1) per subject report;
- confirm adequate breast milk/infant formula is available to feed the infant after first dose of IMP (Visit T1) through Day 13 (Visit FU1) per subject report;
- adverse event review;
- concomitant medicine review;
- weight;

- vital signs;
- urine pregnancy test;
- predose breast milk collection (≤1 hour before IMP administration);
- predose blood sample for chemistry and hematology;
- predose blood sample for plasma PK;
- administer first dose of IMP;
- dispense IMP for self-administration on Day 2 through Day 5;
- provide Study Drug Diary; and
- schedule optional lactation consultant visit.

The IMP will be administered by study staff only after the predose breast milk collection, predose chemistry and hematology, and predose plasma PK sample are collected. Subjects must be reminded to not feed their infant breast milk produced after the first dose of IMP through Day 13 of the study.

Subjects will be instructed to take IMP at the same time (± 2 hours) every day with or without food for Day 2 though Day 5 and to complete the Study Drug Diary.

10.3.3 Treatment Day 2 through Day 5

Study staff will contact the subject by phone to conduct the following:

- adverse event review;
- concomitant medication review;
- confirm subject is taking IMP appropriately;
- instruct subject to complete the Study Drug Diary;
- confirm subject is maintaining adequate breast milk production (document duration of weaning, if applicable) per subject report;
- confirm subject is discarding breast milk produced after the first dose of IMP through Day 13 per subject report;
- confirm adequate stored breast milk and/or infant formula is available to feed the infant through Day 13 of the study per subject report; and
- schedule optional lactation consultant visit.

10.3.4 Treatment Day 5 through Day 7 (Visit T2)

10.3.4.1 Treatment Day 5 (Evening)

Subjects will check-in to the CRU on the evening of Day 5 for 2 overnights. With Sponsor approval, the subject may check-in to the CRU the morning of Day 6.

Subjects will return IMP to the study staff prior to the following assessments:

- adverse event review;

- concomitant medication review;
- review of Study Drug Diary and assessment of IMP adherence (if subject missed a dose or discontinued IMP, refer to Section 9.4);
- confirm subject is maintaining adequate breast milk production (document duration of weaning, if applicable) per subject report;
- confirm subject is discarding breast milk produced after the first dose of IMP through Day 13 per subject report; and
- confirm adequate stored breast milk and/or infant formula is available to feed the infant through Day 13 of the study per subject report.

10.3.4.2 Treatment Day 6

The 24-hour breast milk collection will start the morning of Day 6 and end the morning of Day 7. The following assessments/procedure will be performed prior to the initiation of the 24-hour breast milk collection:

- adverse event review;
- concomitant medication review; and
- subject will pump both breasts with an electric pump until empty prior to administration of the last dose of IMP.

Once both breasts have been completely emptied on the morning of Day 6, Cohort 1 subjects will receive the Day 6 dose of bempedoic acid and Cohort 2 subjects will receive the Day 6 dose of bempedoic acid/ezetimibe FCDP. Breast milk will be collected from each subject over the next 24 hours using an electric pump at 3, 6, 9, 12, 16, 20 and 24 hours (±30 minutes) after Day 6 dose administration.

At each collection time point, subjects will pump both breasts until empty, breast milk collected from each breast will be mixed together and the total volume measured and recorded. Breast milk from each time point will be stored according to procedures outlined in the Laboratory Manual and Section 11.1.

10.3.4.3 Washout Day 7 (after completion of 24-hour breast milk collection)

The following assessments will be performed after the 24-hour milk collection time point:

- adverse event review;
- concomitant medication review;
- physical exam;
- weight;
- vital signs;
- urine pregnancy test;
- collect blood sample approximately 24 hours after Day 6 dosing for PK and safety laboratory samples;

- confirm subject is discarding breast milk produced after the first dose of IMP through Day 13 per subject report;
- confirm adequate stored breast milk and/or infant formula is available to feed the infant through Day 13 of the study per subject report; and
- schedule optional lactation consultant visit.

Once all assessments are complete the subject will be discharged from the CRU.

10.3.5 Washout Day 13 (+ 3 days)/End of Study (Visit FU1)

On Day 13, all subjects will be contacted by phone as a post-treatment follow up visit to review:

- adverse event review;
- concomitant medication review;
- confirm subject discarded breast milk produced after the first dose of IMP through Day 13 per subject report;
- instruct subjects they may resume feeding breast milk currently being produced;
- document subject's intent to resume breastfeeding; and
- schedule optional lactation consultant visit for subjects who desire to re-establish breastfeeding.

10.3.6 Serious Adverse Event Follow-up (SAE FU) and Resumption of Breast-Feeding Day 43 (+ 5 days) (Visit FU2)

Study staff will contact subjects by phone 30 days (Day 43) after FU1 to assess for SAEs and if the patient was able to resume breastfeeding (if intended) without problems.

10.4 Discontinuations

10.4.1 Subjects Inadvertently Enrolled

The inclusion and exclusion criteria for enrollment must be followed exactly and completely. If a subject who does not meet enrollment criteria is inadvertently randomized, the Sponsor should be contacted within 24 hours of identification to determine if the subject should continue in the study.

10.4.2 Permanent Discontinuation of Investigational Medicinal Product

There may be a situation where it is necessary for a subject to discontinue IMP. The Investigator should contact the Sponsor to determine if the subject should be replaced in the study. The subject will be instructed that a 7-day washout is necessary prior to resuming breastfeeding the infant. All Day 7 assessments except the 24-hour PK blood sample and breast milk collection should be performed for early termination.

10.4.3 Subject Discontinuation from the Study

If the subject discontinues prior to completing the study, the Sponsor should be contacted. If possible, an early discontinuation visit should be conducted. All Day 7 assessments except the 24-hour PK blood sample and the 24-hour breast milk collection should be performed. The subject will be permanently discontinued both from the IMP and from the study at that time. The subject will be instructed that a 7-day washout is necessary prior to resuming breastfeeding their infant breast milk produced while on IMP. If the subject discontinues prior to completing the 24-hour breast milk collection in the CRU, the subject will be replaced.

10.4.4 Subjects Lost to Follow-Up

A subject would be considered potentially lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

10.4.5 Discontinuation of Study Sites or the Study

The Sponsor may suspend enrollment or discontinue a site at any time. A written statement will be provided to the Investigator, the IRB, and regulatory authorities, if required.

Possible reasons for site discontinuation include, but are not limited to:

- unsatisfactory enrollment with respect to quantity or quality;
- inaccurate or incomplete data collection on a chronic basis;
- falsification of records;
- failure to adhere to the protocol; and/or
- lack of study oversight by the Principal Investigator and/or designee.

If any serious or nonserious AEs have occurred at such a clinical site, all documentation relating to the event(s) must be obtained.

The Sponsor, in consultation with the IRB Chair, will retain responsibility for discontinuation of the study. The study will be discontinued if necessary, for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

11. PHARMACOKINETIC ASSESSMENTS

11.1 Breast Milk Sample Collection and Processing

Breast milk will be collected using an electric pump. Breast milk samples will be collected within 1 hour before IMP dosing (predose) on Day 1 and on Day 6 at 3, 6, 9, 12, 16, 20 and 24 hours (±30 minutes) after IMP dosing on Day 6. Subjects will be instructed to completely empty both breasts at each sampling time point. At each sampling time point, milk collected from each breast will be mixed together and the total volume will be measured and recorded. From each combined sample 2 aliquots (approximately 5 mL) of breast milk will be transferred to appropriately labeled tubes and stored at or below -70° Celsius within 30 minutes of collection. Breast milk samples from each time point will be stored according to procedures outlined in the Laboratory Manual.

11.2 Blood Sample Collection and Processing

Blood samples for PK analysis will be collected predose on Day 1 and on Day 7 at 24 hours (±30 minutes) after Day 6 IMP administration.

PK samples from each time point will be stored according to procedures outlined in the Laboratory Manual.

12. ASSESSMENT OF SAFETY

12.1 Safety Parameters

At all site visits, Investigators will review all safety information including vital signs, AEs, SAEs, and concomitant medications, and will ensure that the collected data are recorded into the appropriate eCRF. Additionally, laboratory samples will be collected at screening, predose on Day 1, and on Day 7 after completion of the 24-hour breast milk collection and sent for analysis. The Investigator will review the results to ensure continued subject safety while participating in the study.

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor or its designee, if appropriate.

The Investigator is responsible for the appropriate medical care of subjects during the study.

The Investigator is responsible for following AEs that are serious or that cause the subject to discontinue before completing the study until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the Investigator.

12.1.1 Demographic Data and Medical History

Demographic data and a complete medical history will be obtained from the subject. For medical history, conditions and surgeries that are relevant and/or clinically significant should be captured with at least a start date (month and year) and whether the condition is ongoing or resolved. In addition, a postpartum history from the recent pregnancy, inclusive of gestational age at delivery, date of delivery, stage of lactation, length of time postpartum, extent of use of infant formula, and smoking and alcohol intake will be obtained.

12.1.2 Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) is evaluated during screening using the MDRD Study equation (Levey, 2006). Subjects with an eGFR <30 mL/min/1.73 m^2 will not be eligible to participate in the study.

eGFR (mL/min/1.73 m^2) = 175 × (serum creatinine)$^{-1.1.54}$ × (Age)$^{-0.203}$ × 0.742 (if female) × 1.212 (if African American).

12.1.3 Child-Pugh Classification for Assessment of Liver Disease

Child-Pugh classification is evaluated during screening. Please refer to Appendix 2. Subjects classified as Child-Pugh Class B or Class C are not eligible to participate in the study.

12.1.4 Vital Signs

Vital signs will include diastolic blood pressure (DBP) and systolic blood pressure (SBP) as well as heart rate.

Vital signs will be collected prior to blood collection. Blood pressure and heart rate will be measured using a calibrated, fully automated machine with a cuff that is appropriate to the size of the subject's upper arm. If a fully automated machine is not available, BP may be measured manually. The same method (either automated or manual) and the same arm (right or left) must be used throughout the study. The subject should be in a seated position with feet touching the

floor. Subjects should be seated quietly for several minutes in a chair with their backs supported, their feet flat on the ground, and their arms bared and supported at heart level.

12.1.5 Weight, Height, and Body Mass Index

Body weight will be measured on a calibrated scale after voiding. Height will be measured using standard clinic procedures.

Body mass index (BMI) will be calculated systematically using the formula:

BMI (kg/m^2) = weight in kg/(height in meters)^2

12.1.6 Physical Examination

Physical examinations (PE) will include an assessment of the following:

- general appearance;
- skin;
- eyes, ears, nose, and throat;
- head and neck;
- extremities;
- musculoskeletal examination;
- respiratory examination;
- cardiovascular assessment, including rhythm and presence of cardiac abnormalities;
- abdominal examination;
- neurologic examination including documentation of the presence of abnormalities in mental status and motor and sensory function; and
- any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences.

Documentation of the PE findings will be included in the source documentation at the clinical site. Significant findings at Visit S1 will be recorded on the Medical History/Current Medical Conditions page of the eCRF. Only changes from Visit S1 PE findings that meet the definition of an AE will be recorded on the AE page of the eCRF.

12.1.7 Clinical Laboratory Tests

12.1.7.1 Clinical Laboratory Parameters (Safety)

Safety laboratories will be collected at screening (Visit S1), predose on Day 1 (Visit T1) of the study, and on Day 7 (Visit T2) after completion of the 24-hour breast milk collection. Subjects will be in a seated position during the blood collection. Clinical laboratory parameters and tests will include those listed in Table 2 and instructions are in the Laboratory Manual.

Table 2: Safety Laboratory Parameters

<table>
<tr><th colspan="2">Clinical Laboratory Tests</th></tr>
<tr><td>Hematology:
hematocrit (Hct)
hemoglobin (Hgb)
mean corpuscular hemoglobin (MCH)
mean corpuscular hemoglobin concentration (MCHC)
mean corpuscular volume (MCV)
platelet count
red blood cell (RBC) count
white blood cell (WBC) count with differentials</td><td rowspan="2">Clinical Chemistry:
albumin (Alb)
alkaline phosphatase (ALP)
alanine aminotransferase (ALT; SGPT)
aspartate aminotransferase (AST; SGOT)
blood urea nitrogen (BUN)
calcium (Ca)
carbon dioxide (CO2)
chloride (Cl)
creatinine
creatine kinase (CK)
glucose
lactate dehydrogenase (LDH)
phosphorus
potassium (K)
sodium (Na)
total bilirubin (TB) and direct bilirubin
total protein
uric acid</td></tr>
<tr><td>Serology:
hepatitis B surface antigen (HBsAg)
hepatitis C virus antibody (HCV-Ab)
HIV antigen/antibody</td></tr>
<tr><td>Pregnancy Testing:
serum pregnancy (Visit S1 only)
urine pregnancy (Visits T1 and T2 [Day 7] only)</td><td rowspan="3">Coagulation Parameters (to assess Child Pugh Classification of Liver Disease at screening):
prothrombin time
international normalized ratio (INR)</td></tr>
<tr><td>Urine drug and alcohol screen:
alcohol
amphetamines
barbiturates
benzodiazepines
cocaine (metabolite)
methadone
phencyclidine
opiates
tetrahydrocannabinol (THC)/cannabinoids</td></tr>
</table>

12.1.7.2 Sample Collection

Clinical safety laboratory samples will be collected by appropriate clinical site personnel and analyzed at the central laboratory according to site specific procedures.

12.1.7.3 General Monitoring and Management of Abnormal Clinical Laboratory Assessments

It is the Investigator's responsibility to review the results of all laboratory tests as they become available and to sign and date the review. For each laboratory test result outside of the laboratory normal reference range, the Investigator needs to ascertain if this is a clinically significant change from baseline for the individual subject, with baseline defined as the last value or observation before the first dose of IMP. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test.

If a laboratory value is determined to be abnormal and is a clinically significant change from baseline for the subject, the Investigator should determine if it qualifies as an AE (Section 13.2.3), and if yes, an appropriate eCRF will be completed. All clinically significant laboratory abnormalities occurring during the study that were not present at baseline should be followed and evaluated with additional tests if necessary, until diagnosis of the underlying cause or resolution.

12.1.7.4 Total Blood Volume of Clinical Laboratory Samples

The total number of venipunctures and total volume of whole blood collected during the study will be limited to that needed for safety and PK. Total whole blood volume collected over the study duration is not to exceed approximately 65 mL for each subject.

13. ADVERSE AND SERIOUS ADVERSE EVENTS

13.1 Adverse Events

13.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, including control, which does not necessarily have a causal relationship with treatment. The Investigator is responsible for ensuring that any AEs observed by the Investigator or reported by the subject are recorded in the subject's medical record.

An AE can be:

- any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product,
- any new disease or exacerbation of an existing disease, or
- any deterioration in nonprotocol-required measurements of laboratory value or other clinical test (e.g., ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from IMP.

13.1.2 Reporting for Adverse Events

All AEs occurring during the course of the study (starting from signing informed consent to the end of study) will be collected on the AE eCRF. Subjects should be instructed to report any AE that they experience to the Investigator. Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF; however, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion) should be recorded as an AE, not the procedure.

Any medical condition already present at screening or baseline should not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as AEs. The Investigator will exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Analyses of certain AEs will be performed in this study for reasons either associated with other lipid-lowering therapies or where deemed important based on nonclinical or clinical data. These

events include the following: hepatic events, musculoskeletal events, diabetes and glycemia, hypoglycemia associated with metabolic acidosis, renal impairment, neurocognitive events, atrial fibrillation, and tendon rupture/tendinopathy.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the IMP. For each AE, the following information will be recorded:

- description of the event (e.g., headache);
- date of onset;
- date of resolution (or that the event is continuing);
- action taken as a result of the event;
- seriousness of the event;
- severity of the event;
- outcome of the event; and
- Investigator's assessment of relationship to IMP.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (e.g., fever, elevated white blood cells [WBC], cough, abnormal chest x-ray, etc., can all be reported as "pneumonia").

The Investigator will carefully evaluate the comments of the subject and the response to treatment in order that they may judge the true nature and severity of the AE. The question of the relationship of AEs to IMP administration should be determined by the Investigator or study physician after thorough consideration of all facts that are available.

13.1.3 Severity

It is the Investigator's responsibility to assess the intensity (severity) of an AE.

The severity of the AE will be characterized as mild, moderate, or severe according to the following definitions:

- Mild: Events are usually transient and do not interfere with the subject's daily activities.
- Moderate: Events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe: Events interrupt the subject'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.

Note: a severe AE need not be serious and an SAE need not, by definition, be severe.

13.1.4 Relationship

It is the Investigator's responsibility to assess the relationship between the IMP and the AE. The degree of "relatedness" of the AE to the IMP may be described using the following scale:

- Not Related: No temporal association; other etiologies are likely the cause.
- Unlikely: While cannot be definitively ruled as not related to IMP, a causal association is remote, and other etiologies are more likely to be the cause. For reporting and summarization, events assessed as Unlikely to be related to IMP will be considered as Not Related to IMP.
- Possible: Temporal association, but other etiologies are likely the cause; however, involvement of the IMP cannot be excluded.
- Probable: Temporal association, other etiologies are possible but unlikely. The event may respond if the IMP is discontinued.
- Definite: Established temporal association with administration of the IMP with no other more probable cause. Typically, the event should resolve when the IMP is discontinued and recur on re-challenge.

13.1.5 Monitoring and Follow-up of Adverse Events

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator. All follow-up results are to be reported to the Sponsor personnel or the authorized Medical Monitor. Any actions taken and follow-up results must be recorded either on the appropriate page of the eCRF or in appropriate follow-up written correspondence, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests must be repeated at appropriate intervals until final resolution or stabilization of the event(s).

Subjects with AEs related to IMP that are ongoing at study discontinuation or completion must be followed until resolution or for 30 days after study completion, whichever comes first, with the exception of subjects reporting SAEs (Section 13.2.4).

13.2 Serious Adverse Events

13.2.1 Definition of Serious Adverse Event

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions;

- is a congenital anomaly/birth defect; or
- an important medical event.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

13.2.2 Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- preplanned or elective hospitalization including social and/or convenience situations (e.g., due to inclement weather), or
- overdose of either Esperion IMP or concomitant medication unless the event meets SAE criteria (e.g., hospitalization); however, the event should still be captured as a nonserious AE on the appropriate eCRF page.

13.2.3 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the Investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the corresponding laboratory. In some cases, significant changes in laboratory values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the IMP is made as a result of the abnormality;
- intervention for management of the abnormality is required; or
- at the discretion of the Investigator should the abnormality be deemed clinically significant.

13.2.4 Reporting Serious Adverse Events

All SAEs occurring from the time of informed consent of a subject until 30 days following completion or discontinuation of study must be reported by the Principal Investigator or designee to the Safety Contact within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. All SAEs that the Investigator considers related to IMP that occur after the 30-day follow-up period of the study must be reported to the Sponsor.

To report an SAE, complete the electronically provided SAE form in the EDC system and submit it to the Safety Contact. Paper SAE form should only be used in case of EDC system outage. Principal Investigator or designee should complete the SAE form on paper and fax it to the number listed on the form or email it to drugsafety@esperion.com within 24 hours of becoming aware of the occurrence.

The Investigator is required to submit SAE reports to the IRB in accordance with local requirements. All investigators involved in studies using the same IMP will receive any safety alert notifications for onward submission to their local IRB as required.

All SAEs should be recorded on the eCRF and source documents. Criteria for documenting the relationship to IMP and severity will be the same as those previously described.

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to designated Safety Contact.

The Sponsor (and/or legally transferred designee) will report SAEs and suspected and unexpected serious adverse reactions (SUSARs) as required by regulatory authorities, IRBs, and investigators/institutions in compliance with all reporting requirements according to local regulations, laws, and GCPs. The Investigator should notify the appropriate IRB of SAEs occurring at the site and other AE reports received from the Sponsor, in accordance with local procedures and statutes.

13.2.5 Reporting of Subject Death

The death of a subject during the study or within 30 days following her completion of the study, regardless of the cause, must be reported as detailed in Section 13.2.4.

13.2.6 Reports of Pregnancy

Although not considered an SAE (unless an event occurs with a serious outcome), pregnancy information on subjects will be collected by the designated Safety Contact. If a subject should become pregnant during the study, the Principal Investigator or designee must contact the Safety Contact within 24 hours of the Principal Investigator or designee first becoming aware of the pregnancy.

To report a pregnancy, the pregnancy information should be recorded on the Clinical Pregnancy Report Form and sent to the Safety Contact via fax number listed on the form or email (drugsafety@esperion.com) within 24 hours of becoming aware of the pregnancy.

Additionally, the subject's pregnancy should be followed through to its conclusion with the outcome recorded on the Pregnancy Outcome Form and sent to the Safety Contact using either the email or fax noted previously. Please call the designated Safety Contact for assistance or questions.

Subjects who become pregnant will discontinue IMP immediately and will continue to be followed until the pregnancy is completed.

13.2.7 Reports of Infant Exposure to Investigational Medicinal Product via Breast Milk

Infant exposure to IMP via breast milk will be treated as an AE for the infant and should be reported to the designated Safety Contact. If a subject feeds her infant breast milk produced after the first dose of IMP through Day 13 of the Washout Period of the study, the Principal Investigator or designee must contact the Safety Contact to report this incident.

To report infant exposure to IMP via breast milk, the exposure information should be recorded on the Clinical Pregnancy Outcome Form and sent to the Safety Contact via fax number listed on the form or email (drugsafety@esperion.com) within 24 hours of becoming aware of the exposure.

Any additional AEs or SAEs experienced by the infant should be reported as per Section 13, and the infant should then be followed according to the guidance specified in Section 13.1.5, Monitoring and Follow up of Adverse Events or Section 13.2.4, Reporting of Serious Adverse Events, accordingly. Please contact the designated Safety Contact for assistance or questions.

14. STATISTICS

14.1 General Considerations

The statistical analysis described in this section will be performed as further outlined in a separate Statistical Analysis Plan (SAP). The SAP will supersede the protocol in the event of any difference between the 2 documents in data analysis and the protocol will be amended of appropriate. Statistical analyses in this study will be descriptive in nature. No statistical inference is planned. Subject disposition, demographics, and baseline characteristics will be summarized. Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, first and third quartiles, minimum, and maximum. Summary statistics for PK parameters will also include geometric mean and coefficient of Variation (CV) (%). For categorical variables, the frequency and percentage will be given.

14.2 Determination of Sample Size

A minimum sample size of 16 (8 subjects who receive bempedoic acid [Cohort 1]and 8 subjects who receive bempedoic acid/ezetimibe FCDP [Cohort 2]) evaluable subjects (who complete the 6-day treatment period and the 24-hour breast milk collection in the CRU) is planned for this study. Subjects who are randomized but do not complete the 24-hour breast milk collection in the CRU will be replaced with a new subject on the same treatment to ensure 8 evaluable subjects in each cohort for the final analyses.

The sample size was not based on empirical or hypothesis testing criteria. The sample size was based on clinical and regulatory considerations and precedence in previous ETC-1002 studies ([redacted]). The sample size is considered sufficient to address the primary objectives of the study.

14.3 Analysis Population

14.3.1 Safety Population

The Safety Population (SP), used for all the safety summaries, is defined as all subjects who received at least 1 dose of IMP.

14.3.2 Pharmacokinetic Population

The PK Population will include all subjects who complete the 24-hour breast milk collection after IMP administration on Day 6.

14.3.2.1 Primary Analyses

- Daily infant dosage and RID of bempedoic acid will be summarized for Cohort 1 subjects who receive once daily bempedoic acid for 6 consecutive days.
- Daily infant dosage and RID of bempedoic acid and ezetimibe will be summarized for Cohort 2 subjects who received once daily bempedoic acid/ezetimibe FCDP for 6 consecutive days.
- RID will be calculated as the ratio of total infant dose per kg body weight and maternal dose per kg body weight, multiplied by 100.

14.3.2.2 Secondary Analyses

The PK parameters of bempedoic acid, ezetimibe, and metabolites (ESP15228, bempedoic acid glucuronide, and ezetimibe-glucuronide) in mature breast milk will be calculated using standard noncompartmental methods, including:

- breast milk AUC over the 24-hour collection interval;
- average milk concentration based on milk AUC;
- peak and trough milk concentrations as well as time to reach peak milk concentrations; and
- plasma concentrations at 24 hours after the last dose on Day 6.

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix™ WinNonlin® Version 6.4 or higher (Certara USA Inc.).

Descriptive statistics will be provided for the PK parameters.

Other parameters may be added as appropriate; the final PK parameters reported will be detailed in the SAP.

14.4 Safety Analyses

General safety data in this study includes AEs, clinical laboratory parameters, PEs, vital signs, and body weight.

Treatment-emergent AEs (TEAEs) are defined as AEs that begin or worsen after randomization and the first dose of IMP through Day 13. TEAEs will be summarized by System Organ Class (SOC), Preferred Term, and severity. Serious TEAEs, IMP-related TEAEs, TEAEs leading to withdrawal of IMP, and deaths will be also summarized.

Clinical laboratory parameters including hematology and blood chemistry, PE findings, vital signs, and body weight will be summarized and listed using descriptive statistics.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1 Study Monitoring

The Sponsor (or its authorized representative) has the obligation to follow this study closely to ensure that the study is conducted in accordance with the protocol, International Conference on Harmonisation (ICH) and GCP guidelines, national and international regulatory requirements, and the current Declaration of Helsinki throughout its duration by means of personal visits to the Investigator's facilities and other communications.

These visits will be conducted to evaluate the progress of the study, verify the rights and well-being of the subjects are protected, and verify the reported clinical study data are accurate, complete, and verifiable from source documents. This includes review of ICFs, results of tests performed as a requirement for participation in this study, and any other medical records (e.g., laboratory reports, clinic notes, IMP dispensing log, pharmacy records, subject-completed diaries, or telephone logs) required to confirm information contained in the eCRFs.

The monitoring strategy for the study foresees a risk-based monitoring approach, in line with the relevant FDA recommendations and will be described in detail by the study specific risk-based monitoring plan.

A monitoring visit should include a review of the essential clinical study documents (regulatory documents, case report forms, medical records and source documents, drug disposition records, and subject ICFs, etc.) as well as discussion on the conduct of the study with the Investigator and staff.

The monitor should conduct these visits as frequently as appropriate for the clinical study. The Investigator and staff should be available during these visits for discussion of the conduct of the study as well as to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the clinical site by signature and date on the study-specific monitoring log.

15.2 Audits and Inspections

Representatives of the Sponsor or its authorized clinical quality assurance group may visit a clinical site at any time during the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must be respected. The Investigator and clinical site personnel are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or its authorized representative.

The clinical study may also be inspected by the FDA or other regulatory authority to verify that the study was conducted in accordance with protocol requirements, as well as the applicable regulations and guidelines.

In the event the Investigator is contacted by regulatory authorities who wish to conduct an inspection of the clinical site, the Investigator will promptly notify the Sponsor of all such requests and will promptly forward a copy of all such inspection reports.

16. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor (or designee) may conduct a quality assurance audit.

17. ETHICS

17.1 Institutional Review Board Approval

Before initiation of the study, the Investigator must obtain approval or favorable opinion of the research protocol, ICF, and any material related to subject recruitment from an IRB. The IRB must comply with the provisions specified in 21 Code of Federal Regulations (CFR) Part 56, ICH and GCP guidelines, and applicable pertinent state and federal requirements.

IRBs must be constituted according to the applicable laws. It is the responsibility of the clinical site to submit the protocol, IB, subject informed consent, subject recruitment materials (if applicable), and other documentation as required by the IRB for review and approval. A copy of the written approval must be provided to the Sponsor.

The documentation should clearly mention the approval/favorable opinion of the protocol, the subject ICF, and subject recruitment materials (if applicable), including respective version dates. The written approval and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRBs and provided to the Sponsor prior to the release of clinical study supplies to the clinical site and commencement of the study. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

Clinical sites must adhere to all requirements stipulated by their respective IRB. This includes notification to the IRB regarding: protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, aggregate safety reports required by regulatory competent authorities, serious and unexpected AEs, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of final study reports and summaries to the IRB.

It is the responsibility of each clinical site to submit information to the appropriate IRB for annual review and annual re-approval.

The Investigator must promptly inform their IRB of all SAEs or other safety information reported from the subject or the Sponsor.

17.2 Ethical Conduct of the Study

The Investigator agrees, when signing the protocol, to conduct the study in accordance with ethical principles that have their origin in the current revision of the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and policies and procedures as outlined by the ethical requirements for IRB review and ICFs.

The Investigator agrees to allow monitoring and auditing of all essential clinical study documents by the Sponsor or its authorized representatives and inspection by the FDA or other appropriate regulatory authorities. Monitoring and auditing visits by the Sponsor or authorized designee will be scheduled with the appropriate staff at mutually agreeable times periodically throughout the study.

The Investigator will assure proper implementation and conduct of the study, including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperates with monitoring and audits and will demonstrate due diligence

in recruiting and screening study subjects. The Investigator must sign and return to the Sponsor the "Investigator's Signature" page (see Appendix 4) and provide a copy of their current curriculum vitae. For this study and all studies conducted under an investigational new drug application (IND), the Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to the Sponsor (or designee).

17.3 Written Informed Consent

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Subjects must also clearly understand that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures on the Sponsor agreed ICF. Updates to the ICF during the conduct of the study will be communicated by written letter from the Sponsor to the Investigator. The ICF should be provided in the appropriate language of the subject population.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

17.4 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained.

The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor (or designee). If a subject's name appears on any document, it must be redacted and replaced with the subject identifier before a copy of the document is supplied to the Sponsor (or designee). The ICF must include appropriate statements explaining that subject data will be confidential and what actions will be taken to ensure subject confidentiality.

Any other confidentiality requirements specified by the site, IRB, or national or local regulations will be adhered to and detailed appropriately in the ICF.

18. DATA HANDLING AND RECORDKEEPING

18.1 Inspection of Records

Applicable regulations require the Sponsor (or designee) to inspect all documents and records to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) for the subjects in this study. These regulations also allow the Sponsor's records to be inspected by authorized representatives of the regulatory agencies. The Investigator will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

18.2 Retention of Records

In compliance with the ICH/GCP guidelines, the Investigator/Institution agrees to retain and maintain all study records that support the data collected from each subject, as well as all study documents as specified in ICH/GCP, Section 8 Essential Documents for the Conduct of a Clinical Trial. The Investigator agrees to contact the Sponsor before destroying or relocating any study documentation and is expected to take measures to prevent accidental or premature destruction of these documents.

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. The Sponsor must be contacted in writing regarding the name and address of the new person responsible as well as the disposition of document storage. Under no circumstances shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

Essential records (including eCRFs, source documents, IMP disposition records, signed subject ICFs, AE reports, and other regulatory documents) as required by the applicable regulations, must be maintained for 2 years after a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the investigational product.

It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

18.3 Case Report Forms and Study Records

Access to eCRFs will be provided to the clinical site. As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

Study records are comprised of source documents, eCRFs, and all other administrative documents (e.g., IRB correspondence, clinical study materials, and supplies shipment manifests, monitoring logs, and correspondence). A study-specific binder will be provided with instructions for the maintenance of study records.

Source documentation is defined as any hand-written or computer-generated document that contains medical information or test results that have been collected for or in support of the protocol specifications (e.g., laboratory reports, clinic notes, IMP disposition log, pharmacy records, subject sign-in sheets, and telephone logs). All draft, preliminary, and pre-final iterations of a final report are also considered to be source documents (e.g., faxed and hard copy of laboratory reports, faxed and hard copy of initial results, and final report).

The Investigator agrees to allow direct access to all essential clinical study documents for the purpose of monitoring and/or auditing by the Sponsor or its authorized representatives and inspection by the appropriate regulatory authorities.

Data reflecting the subject's participation with the IMP under investigation are to be reported to the Sponsor. The data are to be recorded on the eCRFs and/or other media provided or approved by the Sponsor.

A completed eCRF must be submitted for each subject who receives IMP, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality. The eCRF should not be used as a source document unless otherwise specified by the Sponsor.

Neither the Sponsor nor a service provider contracted to analyze data and complete the study report is permitted to interpret a blank answer; therefore, all fields should be completed. All requested information must be entered on the eCRFs. If an item is not available or is not applicable, this fact should be indicated as not available (N/A) or not done (N/D); do not leave a field blank.

Each set of completed eCRFs must be signed and dated by the Investigator acknowledging review and that the data are accurate and complete. The completed database is to be returned to the Sponsor as soon as practical after completion by the mechanism prescribed for the protocol.

It is essential that all dates appearing on the Sponsor's subject data collection forms for laboratory tests, cultures, etc., be the dates on which the specimens were obtained, or the procedures performed. The eCRFs will be electronically signed by the Investigator and dated as verification of the accuracy of the recorded data. All data collection forms should be completed in a timely manner as defined in the eCRF Completion Guidelines.

19. ADMINISTRATIVE CONSIDERATIONS

19.1 Investigators

The Investigator must agree to the responsibilities and obligations listed below, as specified by the appropriate FDA regulatory requirements or ICH/GCP guidelines:

- agree to conduct the study in accordance with the relevant current protocol;
- agree to personally conduct or supervise the described investigation(s);
- agree to inform any subjects, or persons used as controls, that the IMP are being used for investigational purposes and ensure that the requirements relating to obtaining informed consent and IRB review and approval are met;
- agree to report adverse experiences that occur during the course of the investigation(s);
- read and understand the information in the IB, including the potential risks and side effects of the IMP;
- ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments;
- maintain adequate and accurate records and make those records available for inspection;
- ensure that an appropriate IRB will be responsible for the initial and continuing review and approval of the clinical investigation;
- agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects or others;
- agree to not make changes in the research without IRB approval, except where necessary to eliminate apparent hazards to subjects; and
- comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements.

Refer also to:

- FDA Regulations Related to GCP and Clinical Trials: http://www.fda.gov/oc/gcp/regulations.html
- Guidance and Information Sheets on GCP in FDA-Regulated Clinical Trials: http://www.fda.gov/oc/gcp/guidance.html
- Guidance for IRBs and Clinical Investigators: http://www.fda.gov/oc/ohrt/irbs/default.htm
- Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance: http://www.fda.gov/cder/guidance/959fnl.pdf

19.2 Study Administrative Structure

Please see the Pharmacy Manual for details regarding clinical supply.

Study Management and Data Management:

[redacted]

Central Lab:

[redacted]

Bioanalytical lab:

[redacted]

Statistical Analysis and Programming:

[redacted]

Clinical Research Unit:

[redacted]

Medical and Safety (or Safety Designee):

[redacted]

19.3 Amendments and Study Termination

Changes to the research covered by this protocol must be implemented by formal protocol amendment. All amendments to the protocol must be initiated by the Sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IRB approval. Documentation of amendment approval by the Investigator and IRB must be provided to the Sponsor or its authorized representative. When the change(s) involve only logistic or administrative aspects of the study, the IRB only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the Investigator will contact the Medical Monitor. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Medical Monitor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded on the eCRF and source documents will reflect any departure from the protocol and the source documents will describe the departure and the circumstances requiring it.

The Sponsor reserves the right to terminate this study at any time.

19.4 Financial Disclosure

Prior to the start of the study, investigators will release sufficient and accurate financial information that permits the Sponsor to demonstrate that an Investigator and all study relevant assigned personnel have no personal or professional financial incentive regarding the future approval or disapproval of the IMP such that his or her research might be biased by such incentive.

20. PUBLICATION AND DISCLOSURE POLICY

It is understood by the Investigator that the information and data included in this protocol may be disclosed to and used by the Investigator's staff and associates as may be necessary to conduct this clinical study.

All information derived from this clinical study will be used by the Sponsor (or designee) and therefore, may be disclosed by the Sponsor (or designee) as required to other clinical investigators, to the FDA, EMA, and to other government agencies, or in connection with intellectual property filings or publications. In order to allow for the use of the information derived from this clinical study, it is understood by the Investigator that there is an obligation to provide the Sponsor with complete test results and all data from this clinical study. The Investigator agrees to maintain this information in confidence, to use the information only to conduct the study, and to use the information for no other purpose without the Sponsor's prior written consent (or as otherwise may be permitted pursuant to a written agreement with the Sponsor or its designee).

The results of the study will be reported in a clinical study report prepared by the Sponsor (or designee), which will contain eCRF data from all clinical sites that conducted the study.

The Sponsor or designee will be responsible for preparing the primary manuscript and study results. The Sponsor or designee shall have the right to publish data from the study without approval from the individual investigators. Manuscript(s) and abstract(s) may only be prepared through cooperation between the Sponsor (or designee) and the study Investigator(s). If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review in accordance with the provisions of such Investigator's written agreement with the Sponsor (or designee) before submission for publication or presentation. If requested by the Sponsor in writing, the Investigator will withhold such publication in accordance with the provisions of such agreement.

21. LIST OF REFERENCES

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22. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Period	**Screening Period**	**Treatment Period**				**Washout Period**			**SAE FU**
Visit	**S1**	**T1**	**—**	**T2**		**—**	**—**	**FU1[a]**	**FU2**
Procedure	**Day -42 to -1**	**Day 1**	**Day 2-4**	**Day5**	**Day6**	**Day7[b]**	**Day 8-12**	**Day 13 (+3 days) by phone**	**Day 43 (+5 days) by phone[c]**
Informed consent	X								
Enrollment criteria	X	Predose							
Review of breastfeeding practice	X	Predose							
Adequate breast milk production/weaning	X	Predose	X	X					
Infant able to bottle feed	X	Predose							
Adequate stored breast milk/ formula to feed infant[d]	X	Predose	X	X	X	X			
Demographics	X								
Medical history[e]	X								
Concomitant medications	X	X	X	X	X	X	X	X	
Adverse event review	X	X	X	X	X	X	X	X	X
Physical exam	X					X			
Weight	X	X				X			
Height/BMI	X								
Vital signs[f]	X	X				X			
Serum pregnancy test	X								
Urine pregnancy test		X				X			
Urine drug and alcohol screen	X								
Randomization		X							
Pump breast milk for predose collection at CRU (≤1 hour before IMP administration)		X							
Lactation consultant visit (optional)	X	X	X	X		X	X	X[g]	
Pump and discard breast milk[h]		X	X	X		X[i]	X	X	
Phone call to subject[j]			X	X				X	X
Predose PK blood sample		X							
Clinical lab evaluations[n]	X	X				X			
Dispense IMP		X							

IMP administration at CRU		X			X				
Self-administration of IMP			X	X					
CRU check-in (evening)[k]				X					
IMP return[k]				X					
Study Drug Diary			X	X					
Domicile in CRU				X	X				
Pump breast milk for 0-24 hr. post-dose collection at CRU[l]					X	X			
24-hr (after Day 6 dose) PK blood sample[m]						X			
CRU Discharge (morning)						X			

BMI = body mass index; BP = blood pressure; CRU = clinical research unit; DBP = diastolic blood pressure; FU1 = follow-up visit 1; HR = heart rate; min = minutes; PK = pharmacokinetic; S1 = screening visit 1; SAE FU = serious adverse event follow-up; SBP = systolic blood pressure; T1 = treatment visit 1; T2 = treatment visit 2

[a] Subjects may resume breastfeeding.

[b] All procedures will be completed at early termination except 24-hour PK blood sample and breast milk collection.

[c] Day 43 phone call to follow-up on SAEs and question if patient was able to resume breastfeeding (if intended) without problems.

[d] Subjects must have adequate stored breast milk and/or infant formula available to feed the infant after the first dose of IMP through Day 13 of the study.

[e] In addition to existing medical conditions, medical history should include gestational age at delivery, date of delivery, stage of lactation, length of time postpartum, and smoking and alcohol intake.

[f] Vital signs will include DBP, SBP, and HR. Subject will rest for several minutes prior to assessments.

[g] Lactation consultant visit for subjects who desire to re-establish breastfeeding at the end of study (Visit FU1).

[h] Pump and discard breast milk after the 1st dose of IMP on Day 1 through Day 5 and Day 7 through Day 13.

[i] Discard breast milk produced after completion of the 24hr breast milk collection period.

[j] For Day 2 through Day 5, remind subject to take IMP appropriately and discard breast milk produced after Day 1. If subject misses a dose of IMP contact the Sponsor immediately.

[k] With sponsor approval, the subject may check-in to the CRU the morning of Day 6 and return IMP at that time.

[l] Breast milk collections will be performed using an electric pump at specified intervals (±30 min) over 24 hours at 3, 6, 9, 12, 16, 20, and 24 hours following IMP dosing on Day 6. Both breasts will be emptied completely during each collection. At each sampling time point, milk collected from each breast will be mixed together and the total volume measured. Milk will be stored frozen until time of analysis. The specific timing of the milk sample relative to the IMP dose will be recorded.

[m] A blood sample for PK will be collected on Day 7 approximately 24 hours (±30 min) after IMP administration on Day 6.

[n] Chemistry and hematology at Visit S1, Visit T1 and Visit T2; Serology and coagulation parameters at Visit S1 only.

APPENDIX 2. CHILD-PUGH CLASSIFICATION

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
or			
International normalized ratio	<1.7	1.7-2.3	>2.3
***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

Figure 4 - Child-Turcotte-Pugh Classification for Severity of Cirrhosis
The Child-Turcotte-Pugh (CTP) classification system utilizes two clinical parameters (encephalopathy and ascites) and three laboratory values (bilirubin, albumin, and prothrombin time). Patients are classified as class A, B, or C based on their total points.

Source: Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646-9.

APPENDIX 3. SPONSOR'S SIGNATURES

Study Title: An Open-Label Postmarketing Milk-Only Lactation Study to Evaluate the Concentration of Bempedoic Acid and Bempedoic Acid and Ezetimibe in the Breast Milk of Healthy Lactating Women Administered Therapeutic Doses of Bempedoic Acid or Bempedoic Acid/Ezetimibe Fixed Combination Drug Product (FCDP)

Study Number: 1002FDC-075

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: See attached electronic approval page Date: _____

Name and Credentials:
Title:
Affiliation:

APPENDIX 4. INVESTIGATOR'S SIGNATURE

Study Title: An Open Label Postmarketing Milk-Only Lactation Study to Evaluate the Concentration of Bempedoic Acid and Bempedoic Acid and Ezetimibe in the Breast Milk of Healthy Lactating Women Administered Therapeutic Doses of Bempedoic Acid or Bempedoic Acid/Ezetimibe Fixed Combination Drug Product (FCDP)

Study Number: 1002FDC-075

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed: _____ Date: _____

Name and Credentials:

Title:

Affiliation:

Address:

Phone Number:

APPENDIX 5. SUMMARY OF CHANGES IN AMENDMENT 1 PROTOCOL

SUMMARY OF CHANGES AMENDMENT 1 CLINICAL STUDY PROTOCOL

Study Number:	1002FDC-075
Study Title:	An Open-Label Postmarketing Milk-Only Lactation Study to Evaluate the Concentration of Bempedoic Acid and Bempedoic Acid and Ezetimibe in the Breast Milk of Healthy Lactating Women Administered Therapeutic Doses of Bempedoic Acid or Bempedoic Acid/Ezetimibe Fixed Combination Drug Product (FCDP)
Amendment l Protocol Version Incorporating Current Summary of Changes:	06 June 2023
Preceding Final Protocol Version:	18 August 2021
Investigational Product Name:	Bempedoic acid and bempedoic acid/ezetimibe FCDP

Summary of Changes

The protocol was amended for the following:

- Update IMP packaging description from blister strips to bottles (Section 9).
- Clarify visit windows for Visit FU1 and Visit FU2 (Sections 10.3.5, 10.3.6 and Appendix 1).
- Clarify wording to include investigational vaccines as part of investigational drugs (Sections 2 and 7.2).
- Add section to address concomitant medical procedures (Section 8.3).
- Add serology testing at Visit S1 for the following safety parameters: hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV-Ab) and HIV antigen and antibody (Section 10.3.1, Table 2, and Appendix 1).
- Modify wording to clarify SAE reporting procedures in electronica data capture system (Section 13.2.4).
- Update vendors listed under the Study Administrative Structure (Section 19.2).
- Modify wording to maintain consistency and/or clarity throughout the protocol without impacting study conduct in a meaningful way i.e., defining visits by Visit and Day.
- Other changes to align the document with current Esperion standards, correct typographical errors, formatting updates, modify wording to maintain consistency across bempedoic acid studies, update administrative protocol details, or clarify instructions without impacting study conduct in a meaningful way.