STATISTICAL ANALYSIS PLAN
PROTOCOL 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)

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MODIFICATION HISTORY

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1.0	26 Jun 2024	[redacted]	Not Applicable – First Version.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Specialist Term	Definition
AE(s)	adverse event(s)
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration time curve
BA	bempedoic acid
BLQ	below limit of quantification
BMI	body mass index
COVID-19	coronavirus disease of 2019
CRO	clinical research organization
DBP	diastolic blood pressure
EDC	electronic data capture
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	End-of-Study
EOT	End-of-Treatment
EZE	ezetimibe
FAS	Full Analysis Set
FCDP	fixed combination drug product
FDA	Food and Drug Administration
IMP	investigational medicinal product
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PKS	PK Analysis Set
PT	Preferred Term
RID	relative infant dose
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
TEAE(s)	treatment-emergent adverse event(s)
TFL(s)	table(s), figure(s), and listing(s)

Abbreviation/Specialist Term	Definition
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell
WHO-DDE	World Health Organization – Drug Dictionary Enhanced

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of infant exposure, milk and plasma pharmacokinetic and safety data from healthy lactating women for Protocol 1002FDC-075, entitled *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 1 (*June 6th*, 2023). The SAP will supersede the protocol in the event of any differences between the 2 documents in the plans for data analysis.

Analyses will be conducted using SAS® version 9.4 or higher and Phoenix WinNonlin version 8.4.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objectives of this study are to estimate infant exposure to bempedoic acid (BA) or bempedoic acid and ezetimibe (BA+EZE):

- estimate the daily infant dosage and relative infant dose (RID) of BA in mature breast milk after administration of BA for 6 consecutive days (Cohort 1).
- estimate the daily infant dosage and RID of BA and EZE in mature breast milk after administration of bempedoic acid/ezetimibe fixed combination drug product (FCDP) for 6 consecutive days (Cohort 2).

2.2. Secondary Objective(s)

The secondary objectives of this study are to characterize the excretion of BA or BA+EZE in mature breast milk of healthy lactating women who receive a once daily dose of BA or FCDP for 6 consecutive days:

- determine concentrations of BA (ETC-1002), active metabolite (ESP15228) and inactive metabolite (ETC-1002-glucuronide) in mature breast milk collected over 24 hours from healthy subjects administered BA (Cohort 1) or FCDP (Cohort 2),
- determine concentrations of EZE and active metabolite ezetimibe-glucuronide (EZE-glucuronide) in mature breast milk collected over 24 hours from healthy subjects administered FCDP (Cohort 2).

2.3. Safety:

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

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- Daily infant dosage calculated as the cumulative amount of drug excreted in breast milk on Day 6 of treatment, and
- RID calculated as the ratio of estimated infant daily dose per kg body weight and maternal daily dose per kg of body weight multiplied by 100.

3.2. Secondary Endpoints

BA (ETC-1002), EZE, and metabolites (ESP15228, ETC-1002-glucuronide, and EZE-glucuronide) PK 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_{24h}) over the 24-hour collection interval
- Average milk concentration (Cavg) calculated as AUC_{24h}/24h
- Peak and trough milk concentrations (Cmax, Ctrough), and the time of peak milk concentrations (Tmax)
- Plasma trough concentrations at 24 hours after the last dose on Day 6 (Ctrough)

3.3. Safety Endpoints

- Incidence of the treatment-emergent adverse events
- Clinical safety laboratory assessments (including hematology, blood chemistry, coagulation, and urinalysis), vital signs, and physical examinations.

4. STUDY DESIGN

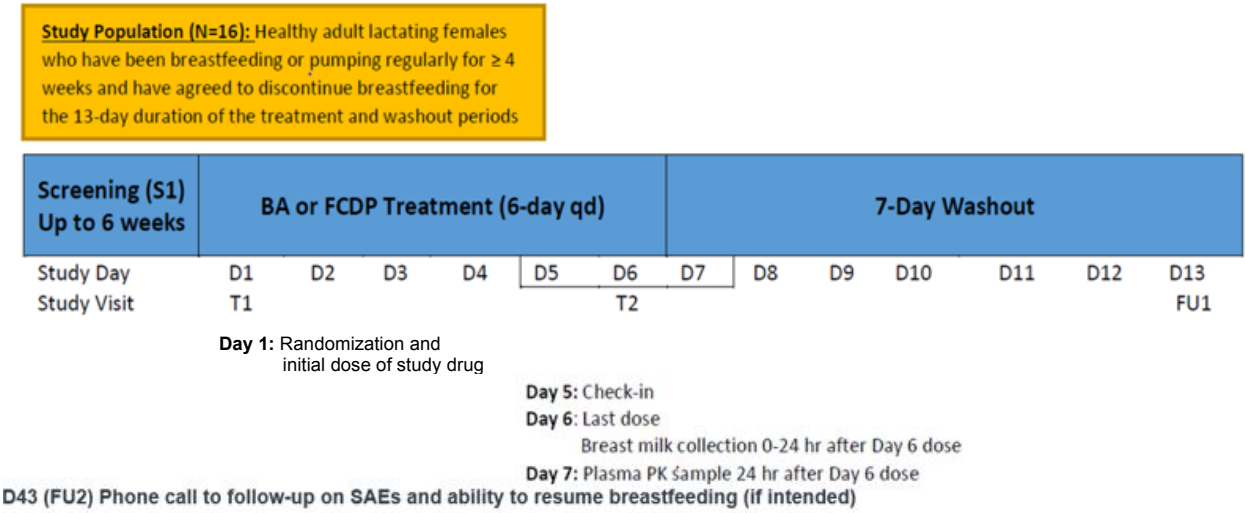
4.1. Overview

This is a Phase 4, open-label study that will estimate the daily infant dosage and RID for BA and FCDP and characterize the excretion of ETC-1002, metabolites ESP15228, ETC-1002-glucuronide, EZE, and EZE-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 BA (Cohort 1) or 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 investigational medicinal product (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. 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.

The study design is presented in Figure 1.

Figure 1: Study Schematic



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.

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 BA (Cohort 1) or 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 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 BA and Cohort 2 subjects will receive the Day 6 dose of 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 (Visit FU2), study staff will contact subjects by phone to assess for SAEs and if the patient was able to resume breastfeeding (if intended).

4.2. Treatment Assignment, Randomization, and Blinding

4.2.1. Randomization and Treatment Assignment

Randomization plan is reviewed and approved before the first subject enrollment and will be archived in eTMF after study database lock. The study site will manually execute the randomization and drug dispense according to Pharmacy Manual.

Sixteen subjects will be randomized in a 1:1 ratio to receive either BA (bempedoic acid 180 mg) (Cohort 1) or FCDP (Cohort 2). The IMP will be taken Day 1 through Day 6 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.

4.2.2. Blinding

This is an open-label study.

5. PLANNED ANALYSES

The following analyses will be performed for this study: Final Analysis

5.1. Interim Analyses

There will be no interim analyses in this study.

5.2. Final Analyses

All PK and safety analyses specified in this SAP will be performed by a CRO.

Additional ad-hoc analyses may be performed as needed.

6. ANALYSIS SETS

Inclusion of subjects in each analysis set will be finalized prior to the database lock of the study. Additional subsets may be explored as needed.

6.1. Full Analysis Set

Full Analysis Set (FAS, same as Safety Population in protocol) will consist of all randomized subjects who receive at least 1 dose of study drug – either BA (Cohort 1) or FCDP (Cohort 2). FAS will be used for summary of disposition, demographics and baseline characteristics, treatment exposure, study drug accountability, postpartum history, infant feeding practice, concomitant medications, and all safety data (including adverse events, clinical laboratory tests, physical examination, vital signs). The summaries will be conducted by cohort.

6.2. PK Analysis Set

The PK Analysis Set (PKS, same as PK population in protocol) will include all subjects in FAS who have at least 1 evaluable post-dosing milk ETC-1002 concentration data point. Data points affected by protocol deviation may be excluded from PK analyses but will remain in the PK concentration data listing.

7. STUDY DEFINITIONS

7.1. Disposition

Study Completion: Subjects who complete study at the End of Study (EOS) visit are considered as achieving study completion.

Treatment Completion: Subjects who complete the End of Treatment (D6/EOT) visit on *Day 6* are considered as achieving treatment completion.

7.2. Reference Start Date and Study Day

Reference Start Date (Day 1) is defined as the date of first dosing of study drug (BA or FCDP).

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Study Day will be calculated as follows:

- If the date of the event is on or after the reference date, then Study Day = (date of event - reference start date) + 1.
- If the date of the event is prior to the reference date, then Study Day = (date of event - reference start date).

The Study Day will be used to show start/stop day of assessments and events (including AEs, prior and concomitant medications). In the situation where the event date is partial or missing as entered in the EDC database, the date will be displayed as such in the listings. Study Day and any corresponding duration(s) will be presented based on the imputations specified in Appendix 2.

7.3. Baseline

Baseline is defined as the last non-missing measurement taken on or prior to initial IMP on Day 1 (including unscheduled assessments), unless otherwise specified.

7.4. Prior and Concomitant Medications

Prior medications are medications which started and ended prior to Day 1.

Concomitant medications are medications that started after Day 1 and continued during the study, or that started before or on Day 1 and continued through Day 1 (“ongoing” at Day 1 or ended after Day 1).

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size

A minimum sample size of 16 (8 subjects who receive BA [Cohort 1] and 8 subjects who receive 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 treated 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 PK analyses. All treated subjects will be in the FAS.

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.

8.1. Number of Centers

The study will be conducted in up to 2 CRUs in the United States. Additional sites may be invited to participate to ensure study timelines are met.

8.2. Coding Dictionaries

Adverse events, medical history diagnoses or signs/symptoms, and concomitant procedures are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 including system organ class (SOC), high level term (HLT) and preferred term (PT).

Prior and concomitant medications are coded using WHO Drug Dictionary (WHO-DD) Global B3 version 01Mar2023.

8.3. General Principles

Descriptive statistics (n, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, and maximum) will be calculated for continuous data. Minimum and maximum will be presented with the same number of decimal places as reported/collected, 1 additional decimal place will be included for mean and median, and 2 additional decimal places will be included for standard deviation.

Categorical data will be summarized using count and percentage based on number of non-missing values. Percentages will be presented with 1 decimal place. The number of missing values will be presented as a separate category when appropriate. Counts of zero in any category will be presented without percentage.

8.4. Missing Data Handling

Unless otherwise specified, missing data will not be imputed.

8.4.1. Imputation of Missing Dates

For adverse events, and for prior and concomitant medications, if the start and/or end dates are incomplete, then the date will appear as-is (partial or missing) in the listings. When a complete

date is needed, e.g., to compute the Study Day, imputation rules specified in Appendix 2 will be used unless otherwise specified. In essence, AEs of uncertain start date will be considered as having started after the first dose of study drug. Medications of uncertain start or end dates will be considered as having started before, or continued after the first dose of study drug, respectively.

8.4.2. PK and Laboratory Data Beyond the Limits of Quantification

Day 1 pre-dose concentrations below the limit of quantitation (BLQ) will be imputed as zero.

Day 6 pre-dose PK concentrations in breast milk were not collected in this study. To facilitate the determination of AUC_{24h} in breast milk, a Day 6 pre-dose concentration value is needed. Since subjects will be near steady state after 6 days of bempedoic acid dosing, the Day 6 pre-dose concentration will be imputed as the trough concentration value on Day 7 at 24 hours post-dose for individual subjects. If a concentration of BLQ is before the last quantifiable value of the subject, it will be marked with an exclusion flag and excluded from analysis. The BLQ concentrations that are at the end of the concentration curve will be imputed by half of the lower limit of quantitation (LLOQ) for the purpose of quantitative summaries.

All PK concentration of BLQ values will be presented as reported, i.e., as "BLQ<(xx.x)" in the listings.

Biomarker and safety laboratory measurements reported as "<X" or ">X" will be imputed as X for the purpose of quantitative summaries, but will be presented as reported, i.e., as "<X" or ">X" in the listings.

9. DISPOSITION AND WITHDRAWALS

All subjects who were screened will be accounted for in this study. Reasons for screen failure will be summarized by pre-defined categories per the Screen Failure eCRF. For screen failures due to inclusion or exclusion criteria violation, the criteria category will be presented in a listing.

The number of subjects in each analysis set, along with study completion status, will be summarized by treatment group as well as overall. Subjects who discontinue from study treatment and/or study will be summarized by discontinuation reason.

A listing of subject disposition will be provided for all randomized subjects, including the treatment and study completion status, and discontinuation reasons, and/or reasons of being excluded from FAS, PKS.

10. PROTOCOL DEVIATIONS

The protocol deviations will be recorded and tracked in the Clinical Trial Monitoring System. All protocol deviations will be reviewed by the clinical team to identify important versus non-important deviations before the final EDC database lock. The final list of protocol deviation will be approved by the study team prior to the EDC database lock and will be used to generate the protocol deviation summary and listing.

For deviations at study entry, subject eligibility will be assessed against the inclusion and exclusion criteria of the protocol. For on-study deviations, compliance with the protocol will be determined via periodical data and monitoring report review.

All protocol deviations will be provided in a listing. Important protocol deviations will be summarized by treatment group and deviation categories for SES.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized by treatment group for the FAS, PKS.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years [yrs])
- Race
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m2)
- BMI group (kg/m2) (<25, 25 ~ <30, or ≥30)

12. MEDICAL HISTORY AND POSTPARTUN HISTORY

12.1. Medical History

Medical information will be presented by Medical Dictionary for Regulatory Activities (MedDRA) SOC and PT for the SES. Medical history conditions are defined as those conditions which started prior to signing of the ICF. Medical history will be coded using MedDRA in most recent version when the study started (Section 8.2).

12.2. Postpartum History of Recent Pregnancy

The postpartum history, including gestation age at delivery and length of postpartum, will be collected at screening and summarized by cohort and for overall FAS.

13. LACTATION STAGE

The lactation stage (lactating/weaning/weaned off) and related information will be collected at Screening and T1 (Day 1) visits. Subject listing of lactation stage, including start date of lactation or weaning, duration of lactation or weaning, and date of weaned off will also be provided.

14. CURRENT FEEDING PRACTICE

Current feeding practice will be collected at Screening and T1 (Day 1) visit.

Number and percentages of subject who produced adequate breast milk, and number and percentages of subject who fed their infant with formula supplementation will be summarized by cohort and for overall on FAS.

The frequency of feeding and the volume of pumped breast milk consumed per day, and the volume of infant formula consumed per day will be summarized by cohort on FAS.

15. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be presented for the SES. In general, the medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class (ATC level 4, anatomical or pharmacological groups), preferred names, and by cohort.

- Prior medications are medications which started and stopped prior to the date of first dose of study drug.
- Concomitant medications are medications that started prior to and continued through the date of the first dose of study drug.

See Appendix 2 for handling of partial dates for prior medications and concomitant medications.

Prior and concomitant medications will be tabulated separately and reported in a subject listing.

15.1. 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.

16. STUDY MEDICATION EXPOSURE AND TREATMENT COMPLIANCE

Study drug exposure duration (days) will be summarized by cohort on FAS.

In addition, estimated compliance with study drug will be presented for the FAS by cohort. The subjects will be grouped as compliant, i.e., those who have 100% of required tablets while on treatment versus non-compliant (<100% compliance).

Per protocol, subjects will take 1 tablet of the study drug once daily, starting from the visit day at which their study drug is initially dispensed (date of Visit T1) to the day of last dose on Day 6. The percentage of compliance will be based on drug accountability data and calculated by the formula using counts of tablets:

Total tablets taken = [tablets dispensed - tablets returned on Day 5] + 1 (if the last dose on Day 6 is administered)

% Compliance = [Total tablets taken] *100 / [treatment duration (days)],

where the protocol-defined treatment duration is 6 days.

The percentage compliance is capped as a maximum of 100% if it exceeds 100%.

Note that subjects who did not receive any study drug or did not report any drug accountability data will be counted as noncompliant (0%).

17. PHARMACOKINETIC (PK) ANALYSIS

17.1. PK Nominal Timepoints

Table 1 Schedule of Dosing and Sample Collection

Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Dosing (once per day)	X	X	X	X	X	X	
Sample	Plasma, Milk					Milk*	Plasma, Milk*
*On Days 6-7, breast milk will be collected during the intervals of 0-3h, 3-6h, 6-9h, 9-12h, 12-16h, 16-20h, and 20-24h after Day 6 dose administration							

PK milk samples will be collected at the following nominal timepoints –

- Visit T1 (Day 1) Pre-dose (≤1 hour before IMP administration)
- Visit T2 (Day 6 and 7) at 3, 6, 9, 12, 16, 20 and 24 hours (±30 minutes) after Day 6 dose administration.

PK plasma samples will be collected at the following nominal timepoints –

- Visit T1 (Day 1) Pre-dose (≤1 hour before IMP administration)
- Visit T2 (Day 7) at 24 hours (±30 minutes) after Day 6 dose administration.

17.2. PK Parameters

The PK parameters listed in the table below are estimated for this study, and used for the primary and the secondary endpoints estimate:

Table 2 PK Parameters

Cohort [IMP]	Specimen	Analytes	PK Parameter
Cohort 1 [BA]	Milk	ETC-1002, ESP15228, ETC-1002-glucuronide	C_{max}, T_{max}, C_{trough}, AUC_{24h}, C_{avg}
	Plasma	ETC-1002, ESP15228, ETC-1002-glucuronide	C_{trough}, M/P ratio*
Cohort 2 [BA/EZE FCDP]	Milk	ETC-1002, ESP15228, ETC-1002-glucuronide, EZE, EZE-glucuronide	C_{max}, T_{max}, C_{trough}, AUC_{24h}, C_{avg}
	Plasma	ETC-1002, ESP15228, ETC-1002-glucuronide EZE, EZE-glucuronide	C_{trough}, M/P ratio*

* M/P ratio = Ctrough $_{(Milk)}$/Ctrough $_{(Plasma)}$ at 24 hours after Day 6 dose administration.

17.3. PK Analysis for Primary Endpoints

The 1st primary endpoint - **daily infant dosage** (mg/day) of BA or EZE will be calculated as the amount of drug in breast milk collected over 24 hours (starting on Day 6 post study treatment) for individual subjects, where the amount of drug in breast milk is calculated as the sum of total drug concentration in each milk collection multiplied by the expressed milk volume in each milk collection.

Daily infant dosage ($Dose_{ij}$) = Σ (C_{ij} x V_{ij}), where

$Dose_{ij}$ = daily infant dose based on collected drug concentration in breast milk and expressed breast milk volume

C_{ij} = drug concentration in breast milk from each collection

V_{ij} = breast milk volume collected at each nominal timepoint

i = nominal timepoints within 24 hours post study treatment on Day 6

j = subjects (8 in each cohort, 16 in total)

- The 2nd primary endpoint - **relative infant dose (RID)** of BA (for Cohort 1 and 2 respectively) or EZE (for Cohort 2 only) equals the percent of the weight-adjusted maternal dosage consumed by infant via breast milk over 24 hours.

  RID (%) = Estimated daily infant dosage (mg/day/kg) / Maternal dosage (mg/day/kg) x 100.

The estimated daily infant dosage will be calculated as the average drug concentration in breast milk over 24 hours after the Day 6 dose administration (C_{avg}) multiplied by 150 mL/day/kg, the estimated standard infant milk intake over 24 hours. Maternal dosage will be calculated as the mean maternal dosage (mg/day per kg baseline body weight determined on Day 1).

Estimated daily infant dosage (mg/day/kg) = C_{avg} (mg/ml) x 150 (ml/day/kg)

Maternal dosage (mg/day/kg) = daily dose of study treatment (mg/day) / baseline body weight (kg)

17.4. PK Analysis for Secondary Endpoints

The secondary endpoints of this study are the following, which are based on PK assessments (see Table 2) for BA (ETC-1002), EZE, and their metabolite (ESP15228, ETC-1002-glucuronide, and EZE-glucuronide) of milk and plasma PK samples.

- Amount excreted in breast milk during each collection period, calculated as the product of analyte concentration and volume of milk collected per collection period.
- Area under the breast milk concentration-time curve (AUC_{24h}) over the 24-hour collection interval. To calculate AUC_{24h}, the initial milk concentration at time equal 0 hours on Day 6 will be set equal to the value of Ctrough for each individual subject.
- Average drug concentration in breast milk (C_{avg}) calculated as AUC_{24h}/24h
- Peak milk concentration (C_{max})
- Time of peak milk concentrations (T_{max})
- Trough milk concentrations at 24 hours after the last dose on Day 6 (C_{trough})
- Plasma trough concentrations at 24 hours after the last dose on Day 6 (C_{trough})

Actual sampling times will be used in the final analyses of individual PK parameters. Predose sampling times will be set to zero. AUC_{24h} will be estimated by noncompartmental analysis (linear up/log down trapezoidal method) and estimates of Cmax and tmax will be reported from observed values. If Cmax occurs at more than one time point, tmax will be assigned to the first occurrence of Cmax.

Cavg in milk will be calculated based on area under the milk concentration-time curve (AUC_{24h}) over the 24-hour collection interval.

C_{avg} (mg/mL) = AUC_{24h} (mg*h/mL) /24h.

If a subject had fewer than 3 data points above LLOQ, AUC_{24h} and C_{avg} will be set to "NE" (Not Evaluable).

M/P ratio is defined as the ratio of milk trough concentration and plasma trough concentration.

M/P ratio = $C_{trough\ (Milk)}/C_{trough\ (Plasma)}$

All the descriptive analyses on PK concentration and PK parameters will be performed upon the PKS.

Collected milk volume, milk concentration of BA and its metabolites will be summarized by nominal sampling timepoints, and by cohort on FAS. Milk concentration of EZE and its metabolite will be summarized by nominal sampling timepoints for Cohort 2 only.

Summary statistics of n, arithmetic mean, standard deviation (SD), CV%, minimum, median, maximum, geometric mean (converting back to the original units), and geometric coefficient of variation (GCV%) will be presented for PK concentration data and PK parameters (AUC_{24h}, C_{avg}, C_{max}, T_{max}, C_{trough}) by cohort in summary tables.

- Geometric mean = exp [mean of log(x)], exponential of mean of log-transformed concentration data.
- Geometric standard deviation (GSD) = exp [SD of log(x)], exponential of standard deviation of log-transformed concentration data.
- GCV% = sqrt [exp (GSD^2) -1] x 100.

The following assessments will also be summarized by cohort:

- Daily infant dosage ($Dose_{ij}$)
- Estimated daily infant dosage
- RID
- M/P ratio

Plots of the following milk concentration-time profiles will be created:

- (A) ETC-1002, (B) ESP15228, (C) ETC-1002-glucuronide on linear scale by cohort.
- (A) EZE, (B) EZE-glucuronide on linear scale for Cohort 2.
- Composite of individual subject (A) ETC-1002, (B) ESP15228, (C) ETC-1002-glucuronide, (D) EZE, (E) EZE-glucuronide on linear scale by cohort.

Box plot of the following parameters from breast milk PK will be created by cohort:

- C_{max}, C_{trough}, C_{avg}, and AUC_{24h} (A) ETC-1002, (B) ESP15228, (C) ETC-1002-glucuronide, (D) EZE, (E) EZE-glucuronide by cohort

All milk and plasma PK concentration data and parameters will be displayed in subject listings.

18. SAFETY ANALYSIS

18.1. General

All summary tables for safety outcomes will be based on the FAS. All adverse event tables will be summarized by cohort. There will be no statistical comparisons between cohort for safety data, unless otherwise specified.

18.2. Adverse Events

18.2.1. Treatment Emergent Adverse Events (TEAEs)

All types of AE summarization described in this section are for TEAEs only, which is defined as AEs that occur or worsen after the first dose of study drug up to the end of the study (Visit Follow-Up 2/Day 43).

Severity is classed as mild, moderate, or severe (increasing severity). TEAEs starting after the first dose of study drug with a missing severity will be classified as severe. If a subject reports a TEAE more than once within the same System Organ Class (SOC) and Preferred Term (PT), then the TEAE with the worst-case severity will be used in the corresponding severity summaries.

Relationship to study treatment, as indicated by the Investigator, is "Unrelated" if the TEAE is "not related" or "unlikely related". A "related" TEAE is defined as a TEAE with a relationship of "possibly related", "probably related", or "definitely related" to study medication. TEAEs with a missing relationship to study medication will be regarded as "related" to study medication.

A TEAE overview summary will be provided for FAS by cohort and for total (Cohort 1 and 2). The following categories will be presented in the AE overview summary:

- Number of subjects with any TEAE
- Number of subjects with any TEAE related to study treatment
- Number of subjects with any SAE
- Number of subjects with any SAE related to study treatment
- Number of subjects with any TEAE leading to study treatment discontinuation
- Number of subjects with any TEAE by highest severity
    - Mild
    - Moderate
    - Severe
- Number of subjects with any AE by strongest relationship with study treatment
        - Related (including definitely related, probably related, possible related, and missing)
        - Unrelated (including unlikely related, not related)

Subject incidence of TEAEs, serious AEs (SAEs), and TEAEs leading to withdrawal of study treatment will be tabulated by SOC and PT in descending order of frequency among the total .

TEAEs that are related to study treatment will be summarized separately. If a subject reports the same TEAE more than once within that SOC/PT, then the TEAE with the worst-case relationship to study treatment will be used in the corresponding relationship summaries.

An AE listing will be provided includes both TEAEs and non-TEAEs.

18.3. Safety Laboratory Evaluations

18.3.1. Safety Laboratory Evaluation

Quantitative laboratory measurements, including hematology, blood chemistry, and coagulation, will be reported with the relevant laboratory reference ranges in Conventional US units and classified as Low/Normal/High by the central lab:

- Low: below the lower limit of the laboratory reference range;
- Normal: within the laboratory reference range (upper and lower limit included); or
- High: above the upper limit of the laboratory reference range.

A list of laboratory assessments to be included in the outputs is included in Appendix 3.

Quantitative lab results at baseline (pre-dose on Day 1/Visit T1) and at end of study 24 hours after the last dose on Day 6 (Day 7/Visit T2) and change from baseline values at Visit T2 will be summarized by cohort. Urinalysis is quantitative and will not be summarized.

The Modification of Diet in Renal Disease (MDRD) equation (Levey 2006) for estimated glomerular filtration rate (eGFR) will be used by the central lab,

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

where creatinine is in mg/dL.

All lab test results will be listed by subject, lab test name, and visit.

18.4. Vital Signs

The following vital signs measurements will be reported for this study:

- Sitting systolic blood pressure (mmHg)
- Sitting diastolic blood pressure (mmHg)
- Sitting heart rate (beats per minute [bpm])

Summaries will be provided by cohort for vital signs data for observed values at baseline and Visit T2 and change from baseline values at Visit T2 .

18.5. Physical Examination

Clinically significant abnormal findings that occur post initial IMP will be reported as TEAE.

Al abnormalities in physical examinations will be presented in a subject listing.

19. REFERENCES

1. Clinical Lactation Studies: Considerations for Study Design. Draft Guidance for Industry (FDA May 2019), Draft Guidance https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design
2. Investigator's Brochure, ETC-1002, v15.5, May 2020
3. Protocol 1002FDC-075 Pharmacy Manual v1.0
4. Report 1002-061. Population Pharmacokinetic/Pharmacodynamic Analysis of Bempedoic Acid and LDL-C Concentration in Healthy Subjects and Patients with Primary Hypercholesterolemia. 31 Aug 2020.

APPENDIX 1. SCHEDULE OF EVENTS

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. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

The following rules will be used to impute partial missing AE start/stop dates:

AE start date	If only Day is missing:	If the AE start year and month are the same as that for the first dose (Day 1) date, then the AE start day will be imputed as the day of first dose date; otherwise, the AE start day will be imputed as the first day of the month.
	If both Day and Month are missing:	If AE start year is the same first dose year, then the AE start Month and Day will be imputed as the Month and Day of first dose date; otherwise, the AE start date will be imputed as 01 January.
	If Year of AE start date is missing, or AE start date is complete missing:	The AE start date will be imputed as the first dose date.
AE end date	If only Day is missing:	If only Day is missing and AE end month and year are the same as the month and year of the EOS date, then use the subject completion date; otherwise, the last day of the month will be imputed.
	If both Day and Month are missing:	If both Day and Month are missing and AE end date year is the same as the year of the EOS date, then the subject completion date will be used to impute. If the year of the AE end date precedes the year of the EOS date, then the AE end month and day will be set to 31 December.
	If the Year of AE end date is missing, or AE end date is completely missing:	If only Year is missing, then the EOS year will be assigned to the end date. If the AE end date is completely missing, then "Ongoing" status will be assigned.

AE = adverse event; EOS = End-of-Study

The following rules will be used to impute partial missing medication dates:

Medication start date	If only Day is missing:	If only Day is missing, then the first day of the month will be assumed.
	If only Day and Month are missing:	If both Day and Month are missing, then January 1 will be assumed.
	If only Year is missing, or date is completely missing:	If only Year is missing, then informed consent signature year will be used to impute. If medication start date is completely missing, then the informed consent signature date or medication end date whichever is earlier, will be used to impute.
Medication end date	If only Day is missing	If only Day is missing, then the last day of the month will be assumed.
	If both Day and Month are missing	If both Day and Month are missing, then the medication end date month and day will be set to December 31.
	If Only Year is missing, or medication end date is completely missing	If only Year is missing, then the year of last visit will be assigned for the end date. If medication end date is completely missing, then "Ongoing" status will be assigned, and the end of study date will be imputed

EOS = End-of-Study

APPENDIX 3. CLINICAL SAFETY LABORATORY TESTS

Hematology	• Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood (RBC) cell count • White blood (WBC) cell count with differential (absolute and %)
Clinical Chemistry (serum, fasting)	• Albumin (ALB) • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO_2) • 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
Urinalysis (Dipstick)	• Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult Blood • pH • Protein • Specific Gravity • Urobilinogen
Coagulation Parameters	• prothrombin time (PT) • international normalized ratio (INR)