STATISTICAL ANALYSIS PLAN

Randomized, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of EP547 in Healthy Subjects and Subjects with Cholestatic or Uremic Pruritus

PROTOCOL NO.: EP-547-101

PRODUCT CODE: EP547

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SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed by Escient Pharmaceuticals, Inc. and has been approved for use on the EP-547-101 study:

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List of Abbreviations

Abbreviation	Description
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
AUC	Area under The Curve
[redacted]	[redacted]
BLQ	Below Limit of Quantification
BUN	Blood Urea Nitrogen
[redacted]	[redacted]
CHB	Chronic hepatitis B
C_{max}	Maximum Plasma Concentration
[redacted]	[redacted]
CP	Cholestatic Pruritus
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of Variation
[redacted]	[redacted]
DBP	Diastolic blood pressure
ECG	12-Lead Electrocardiogram
FE	Food Effect
FC	Fold Change
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HS	Healthy Subjects
INR	International Normalized Ratio
[redacted]	[redacted]
LDL	Low-Density Lipoprotein
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
MAD	Multiple-Ascending Doses
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
nBLQ	Number of Below Limit of Quantification
NC	Not Calculable
NCS	Not Clinically Significant
[redacted]	[redacted]
NK	Not Known
NR	No Results
[redacted]	[redacted]
PD	Pharmacodynamic
[redacted]	[redacted]

Abbreviation	Description
PK	Pharmacokinetic
PT	Preferred Term
RBC	Red blood cells (erythrocytes)
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard Deviation
SD-CP	Single Dose - Cholestatic Pruritus
SD-UP	Single Dose - Uremic Pruritus
S.I.	International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
$t_{1/2}$	Apparent Plasma Terminal Elimination Half Life
T_{max}	Time to maximum concentration
[redacted]	[redacted]
UP	Uremic Pruritus
[redacted]	[redacted]
WBC	White blood cells (leukocytes)
WHO-DD	World Health Organization Drug Dictionary
[redacted]	[redacted]

1. INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of data collected from the EP-547-101 study (Protocol Original dated 17 June 2020).

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

This amendment to SAP is done to incorporate the changes made to the study as per the various revisions of protocol:

- Protocol Amendment 1.0 dated 14 December 2020
- Protocol Amendment 2.0 dated 19 February 2021
- Protocol Addendum 1.0 to Amendment 2.0 dated 19 March 2021

2. PROJECT OVERVIEW

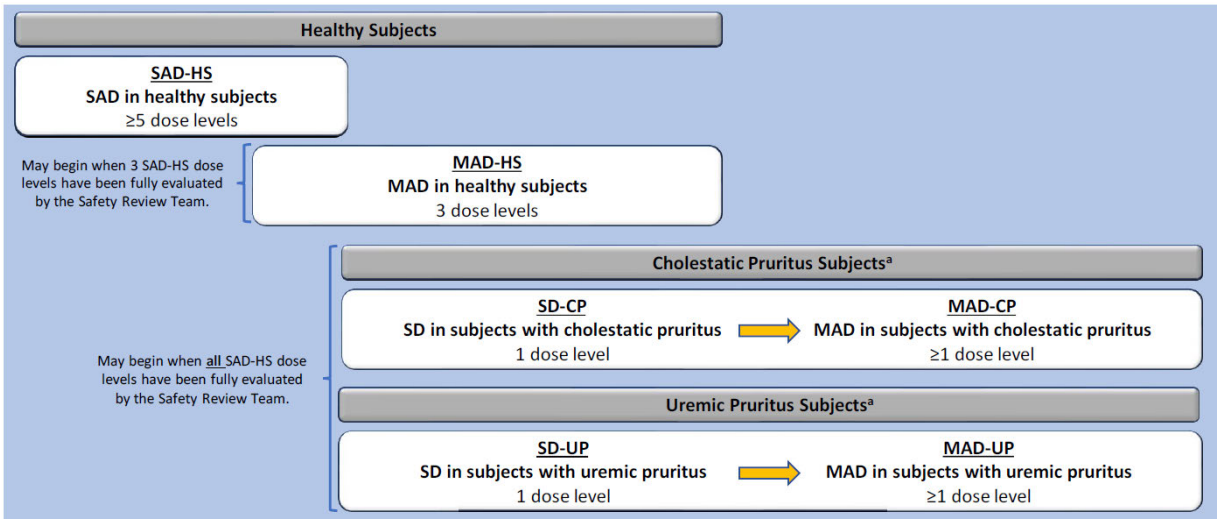
2.1.1 Study Design

This study is a first-in-human, Phase 1, randomized, single and multiple ascending dose (SAD and MAD) study with EP547 in healthy subjects and subjects with cholestatic or uremic pruritus. As shown in Figure 1, each population will include a SAD or single dose (SD) segment followed by a MAD segment for a total of 6 segments (single ascending dose – healthy subject [SAD-HS] and multiple ascending dose – healthy subject [MAD-HS] in healthy subjects [HS]; single dose – cholestatic pruritus [SD-CP] and multiple ascending dose - cholestatic pruritus [MAD-CP] in subjects with cholestatic pruritus [CP]; and single dose - uremic pruritus [SD-UP] and multiple ascending dose - uremic pruritus [MAD-UP] in subjects with uremic pruritus [UP]. Each segment will evaluate at least 1 dose level. Pruritus is not a mandatory requirement for participation in SD-CP or SD-UP.

Although SAD-HS and all of the MAD segments will be conducted in a blinded manner (ie, subjects, Investigator, study-site personnel, and Contract Research Organization [CRO] staff not involved in PK sample analysis or regulatory reporting will be blinded to treatment), the Sponsor, including the Sponsor Medical Monitor, will be unblinded to treatment assignment to assess safety on an ongoing basis.

SAD-HS will evaluate at least 5 dose levels of EP547, establish the highest well-tolerated dose in healthy subjects, and guide MAD dosing in the same population. Evaluation of the first of 3 dose levels for MAD-HS may commence after 3 dose levels from SAD-HS have been fully evaluated by the Safety Review Team. When the results of all dose levels from the SAD-HS segment have been fully evaluated by the Safety Review Team, evaluation of a single dose level for SD-CP and SD-UP may commence. SD-CP and SD-UP will confirm predicted PK concentrations and guide MAD dosing in their respective populations. SD-CP and SD-UP may be conducted in parallel. Evaluation of at least 1 dose level for MAD-CP and MAD-UP may commence when the dose level from the SD segment specific to their population has been fully evaluated by the Safety Review Team. Subjects from the SD-CP and SD-UP segments may screen to determine eligibility for participation in the MAD segment specific to their population.

Figure 1: EP-547-101 Study Designs



2.1.2 Food effect (FE) Sub study

Twelve healthy subjects will participate in this 2-period, unblinded, randomized, crossover food effect sub study to evaluate the PK of a single dose of EP547 administered orally (PO) in a fasted or fed condition. Subjects who participated in SAD-HS or MAD-HS may not participate in FE-HS. Subjects will be randomized in a 1:1 ratio to either Sequence 1 (Fasted for FE Period 1, Fed for FE Period 2) or Sequence 2 (Fed for FE Period 1, Fasted for FE Period 2). The dose level to be tested in FE-HS will be 75 mg, which was selected based on safety and tolerability data and EP547 PK characteristics from SAD-HS and MAD-HS, and from data generated by nonclinical studies.

Doses between the 2 FE Periods must be separated by a minimum of 10 days to allow for washout of study drug.

Fasted Regimen:

EP547 will be administered after an overnight fast for a minimum of 8 hours. Subjects will remain fasted until after the 4-hour PK blood sample is collected.

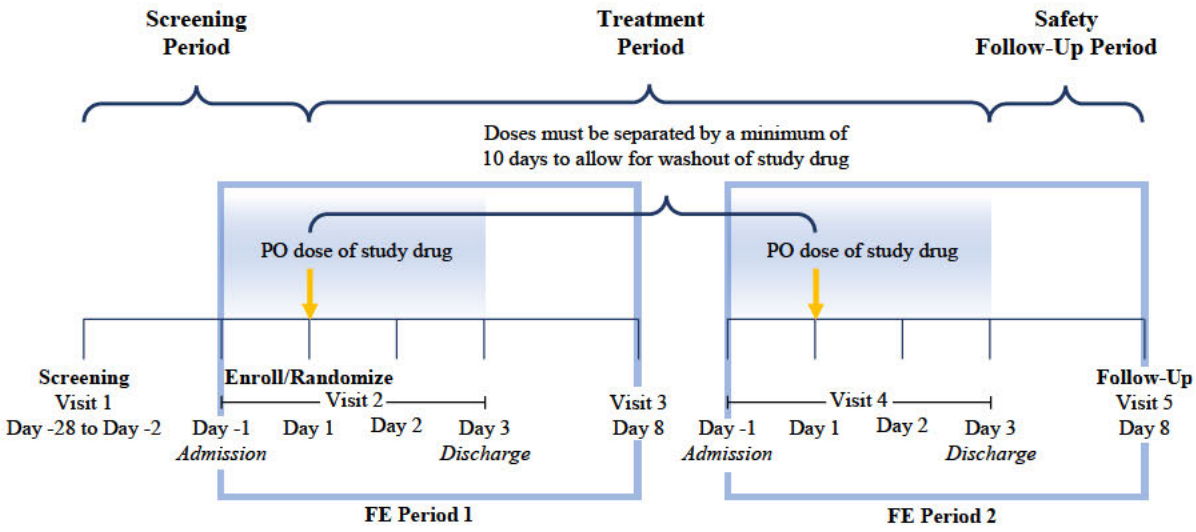
Fed Regimen:

Subjects will fast overnight for a minimum of 8 hours. Approximately 30 minutes before administration of study drug, subjects will consume a high fat/high calorie breakfast and will be instructed to consume the entire meal in 30 minutes or less. Subjects must consume at least 90% of their meal to be eligible for dosing. The start and stop time and percentage of the breakfast consumed will be recorded. Per guidance from the Food and Drug Administration (FDA), the high fat/high calorie meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively (FDA 2002). No other food or drink (other than water as specified above) will be permitted until after the 4-hour PK blood sample is collected.

Both Regimens:

Each meal and/or snack served at the clinic will be standardized, similar in caloric content and composition (except for the high-fat/high calorie breakfast served as part of the fed regimen), and consumed at approximately the same time in each FE Period during confinement.

Figure 2: FE Study design



PO = oral
Shading represents the mandatory period when subjects will be confined to the study site.
Visit 5 (Day 8) is also the Follow-Up visit and is to occur 7 days after the last administration of study drug.

2.2 Objectives

2.2.1 Primary objective

- The primary objective of this study is to evaluate the safety and tolerability of single and multiple ascending doses of EP547 in healthy subjects and subjects with cholestatic or uremic pruritus

2.2.2 Secondary objectives

The secondary objectives of this study are:

- To evaluate the pharmacokinetics (PK) of single and multiple ascending doses of EP547 in healthy subjects and subjects with cholestatic or uremic pruritus
- To assess QT/corrected QT (QTc) interval prolongation risk using EP547 concentration-QT/QTc modeling in healthy subjects (for use at a later development stage, not as a result of a safety signal)

[redacted]

2.3 Endpoints

2.3.1 Primary endpoints

- Adverse events (AEs)
- Clinical laboratory assessments
- Vital signs and body weight
- Standard 12-lead Electrocardiogram (ECGs)
- Physical examinations

2.3.2 Secondary endpoints

- Plasma EP547 and metabolites (as applicable) concentrations
- Plasma PK parameter estimated using noncompartmental analysis (NCA), as appropriate:
  - **SAD** segments: C_{max}, t_{max}, K_{el}, $t_{1/2}$, AUC_{∞}, AUC_t, $\%AUC_{extra}$, CL/F, and Vz/F
  - **MAD** segments: C_{max}, C_{trough}, t_{max}, K_{el}, $t_{1/2}$, AUC_{τ} (as appropriate), AUC_t, CL/F, Vz/F, and Rss
- Urine PK parameters estimated using NCA, as appropriate:
  - SAD-HS segment: Ae, Fe, CLr
- Skin EP547 and metabolites (as applicable) concentrations
- Holter monitoring for 12-lead ECG acquisition and subsequent cardiodynamic analysis

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Plasma PK parameter estimated using noncompartmental analysis (NCA) for the FE segment, as appropriate:
    - C_{max}, t_{max}, K_{el}, $t_{1/2}$, AUC_{∞}, AUC_t, $\%AUC_{extra}$, CL/F, and Vz/F

2.4 Sample Size

No formal sample size calculation has been made. The sample size has been selected to provide adequate information on safety, tolerability, PK, and PD following single and multiple doses of EP547.

80 to 132 subjects are expected to participate in the study, including 64 to 72 healthy subjects, 8 to 30 CP subjects, and 8 to 30 UP subjects:

- 5 to 6 groups of 8 subjects each in SAD-HS
- 3 groups of 8 subjects each in MAD-HS
- 1 group of 6 subjects each in SD-CP and SD-UP (non-randomised)
- 1 to 2 groups of 8 to 12 subjects each in MAD-CP and MAD-UP; up to 6 subjects each from the SD-CP and SD-UP segments will participate in the MAD segment specific to their population if they meet the requirement for pruritus (will be rescreened and allocated a new participant ID following washout)

For FE sub study a sample size of 12 subjects was selected to estimate the effect of food on the PK of EP547.

2.5 Randomization

SAD-HS and all of the MAD segments will be conducted in a blinded manner (i.e., subjects, Investigator, study-site personnel, and Contract Research Organization staff not involved in PK sample analysis or regulatory reporting will be blinded to treatment). The Sponsor, including the Sponsor Medical Monitor, will be unblinded to treatment assignment to assess safety on an ongoing basis.

SD-UP and SD-CP will be open label, with all subjects assigned active treatment (EP547) and do not require randomization.

FE sub study will be open label and randomized.

Furnished below are the details of randomisation in each segment.

- SAD-HS:
    - Up to 5 dose levels (with the flexibility to evaluate a sixth level)
    - 8 participants per group, randomized EP547: Placebo 3:1
    - Sentinel dosing - sentinels randomised EP547: Placebo 1:1
    - Non-sentinel dosing randomised EP547: Placebo 5:1
- MAD-HS:
    - Up to 3 dose levels
    - 8 participants per group, randomized to receive EP547 or placebo for 7 days in a 3:1 ratio
    - No sentinel dosing
- SD-CP/UP:

  - Initiated after all dose levels of SAD-HS have been fully evaluated by the Safety Review Team
  - No randomization, unblinded, 1 dose level each (SD-CP and SD-UP), 6 participants per group

- MAD-CP:
  - 1 dose level (with potential 2nd cohort if required)
  - 8 participants, randomized to receive EP547 or placebo for 7 days in a 3:1 ratio
  - Potential to enroll up to 4 more subjects (for a total of 12)
  - No sentinel dosing

- MAD-UP:
  - 1 dose level (with potential 2nd cohort if required)
  - 8 participants, randomized to receive EP547 or placebo for 7 days in a 3:1 ratio
  - Potential to enroll up to 4 more subjects (for a total of 12)
  - No sentinel dosing

- FE:
  - Single dose of EP547 administered orally (PO) in a fasted or fed condition
  - 12 participants, randomized to one of the two sequence in 1:1 ratio [Sequence 1 (Fasted for FE Period 1, Fed for FE Period 2) or Sequence 2 (Fed for FE Period 1, Fasted for FE Period 2)]

3. STATISTICAL CONSIDERATIONS

Data will be handled and processed per the sponsor's representative (Novotech) Standard Operating Procedures (SOPs), which are written based on the principles of good clinical practice (GCP).

Each study segment (SAD-HS, MAD-HS, SD-CP/UP, MAD-CP/UP, FE) will be presented separately for tables. Listing will include all data separated by segment and dose level (if applicable). For FE segment separate listing will be provided. Novotech will not be responsible to generate any figures for the study.

3.1 General Considerations

All data collected on the electronic case report form (eCRF) will be presented in the data listings and will be listed and sorted by treatment group, participant number and visit, where applicable. All descriptive summaries will be presented by treatment group and nominal visit/time point (where applicable).

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean, SD and median values will be displayed to one more decimal than the source data for the specific variable.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the above mentioned rules.

- PK data: The actual blood sampling dates and times relative to dosing time will be listed by treatment group, participant and nominal sampling time, with time deviation calculated, for all participants with available plasma concentration data, including participants excluded from the PK population. Individual (for each participant) and mean plasma and skin EP547 and metabolites (as applicable) concentrations over time will be displayed graphically in linear and semi-logarithmic plots of concentrations versus time. The actual collection time will be used for individual plasma and skin EP547 and metabolites (as applicable) concentration curves and the nominal time will be used for the plots of mean concentration curves.

  For plasma and skin PK concentration data, the number of non-missing values, number of below limit of quantification (BLQ) values, arithmetic mean, standard deviation, median, minimum, maximum, coefficient of variation (CV%), geometric mean, geometric standard deviation (SD) and geometric coefficient of variation (geo CV%) values will be presented. For the calculation of summary statistics, unrounded data will be used and reported to three significant figures with the exception of n, n BLQ, and CV% which will be presented to the nearest integer and one decimal place, respectively.

  For PK parameter data, the number of non-missing values, arithmetic mean, standard deviation, geometric mean, geometric SD, geometric CV, median, minimum and maximum values will be presented. Individual PK parameters will be presented to three significant figures with the exception of T_{max} which will be presented to two decimal places.

- Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of participants in the relevant analysis population with non-missing data, unless specifically stated otherwise. Percentages will be displayed to one decimal place. Proportions will be displayed to 3 decimal places.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings.

- Assessment windows: All assessments will be included in the data listings and no visit windows will be applied to exclude assessments that were performed outside of the protocol specified procedure windows.
- Result display convention: Results will be center aligned in all summary tables and listings. Participant identifiers visit and parameter labels may be left-aligned if required.
- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:

  Date only: YYYY-MM-DD

  Date and time: YYYY-MM-DD HH:MM

If only partial information is available, unknown components of the date or time will be presented as 'NK' (not known), i.e., '2016-NK-NK'. Times will be reported in military time.

3.2 Key Definitions

The following definitions will be used:

- Baseline: The baseline value is defined as the last available valid (quantifiable continuous or categorical value), non-missing observation for each participant prior to first study drug administration. Repeat and unscheduled assessments will be included in the derivation of the baseline values. [redacted]
- For FE Segment ([redacted]) the baseline value is defined as the last available valid (quantifiable continuous or categorical value), non-missing observation for each participant prior to the study drug administration in each period. Repeat and unscheduled assessments will be included in the derivation of the baseline values. Below table provide the baseline measurement to be considered for each parameter.

Measurement	Period 1	Period 2
Laboratory(Hematology, Chemistry & Urinalysis), Vital Signs and ECG	Pre-dose value captured at Visit 2 Day 1, if missing then value captured at Screening.	Pre-dose value captured at Visit 4 Day 1.

- Change from Baseline: The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/time point and the baseline value.

  The change from baseline value at each post-baseline visit/time point will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at Visit/Time Point – Baseline Value

  The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available and will be treated as missing otherwise.

- Percent Change from Baseline

  Percent Change from Baseline at each post-baseline visit/time point will be calculated for all continuous parameters using following formula.

  % Change from Baseline =100 x [(Post-Dose Visit Value – Baseline) / Baseline]

- Study Day: The study day of an event is defined as the relative day of the event starting with the date of the first study drug administration (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study drug administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration)

For events occurring on or after Day 1, study day will be calculated as:

Study Day = (Date of Event - Date of First Study Drug Administration) + 1

Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

Relative days compared to an alternative reference point will be calculated similarly, but the alternative starting reference start date will be used instead of the date of the first study drug dosing.

- Period Study Day: For FE segment, the Period Study Day of an event is defined as the relative day of the event relative to the previous study drug administration date.

  Period Study Day = (Date of Event – Date of Previous Study Drug Administration) + 1

  If an event occurs prior to the first administration of study drug, period study day will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration)

- Actual Time from First Dose (hours) = (Date/Time of PK Sample collection) – (Date/Time of First Dose on Day 1)
- For FE segment the actual time from first dose (hours) will be derived based on the dosing day in each period.

  ie; Actual Time from First Dose (hours) = (Date/Time of PK Sample collection) – (Date/Time of First Dose on Day 1 in each period)

- Actual Time Deviation (hours) = (Actual PK Sample Collection Time Post Dose) – (Scheduled PK Sample Collection Time Post Dose).
- Prior Medications: Prior medications are defined as any medication where the use was stopped prior to the first administration of the study medication.
- Concomitant Medications: Concomitant medications are defined as any medication (other than the study drug) that was used at least once after the first administration of the study drug. Medications that were stopped on the same date as the first study drug administration will be included as concomitant medications. If a clear determination cannot be made (partial medication end dates) the medication will be classified as concomitant.
- For FE segment concomitant medication will be defined as follows:
  - All medications stopped post study drug administration in Period 1 but prior to study drug administration in Period 2 will be attributed to Period 1 treatment only.
  - All medications started prior to study drug administration in Period 1 and stopped after study drug administration in Period 2 will be attributed to both treatments.
  - All medications started post to study drug administration in Period 2 will be attributed to Period 2 treatment only.
- Treatment Emergent Adverse Events (TEAEs) are defined as adverse events that occurred following the first administration of study medication.
- For FE segment treatment emergent adverse events will be defined as follows:
  - TEAEs that start on or after the study drug administration of Period 2 will be attributed to Period 2 treatment only.
  - TEAEs that start on or after the study drug administration of Period 1 but prior to study drug administration of Period 2 will be attributed to Period 1 treatment only.

  Any change in severity will be seen as a new event and will be allocated to the treatment in the same way.

If only the event start year (and month) is present, the event will be allocated to all treatment with the same start year (and month), unless the event end date clearly indicates that an event did not occur within certain periods.

If complete dates are missing (start and end dates), the event will automatically be classified as an event for all treatment (Period).

3.3 Inferential Analyses

Descriptive statistics will be used to summarize the safety and PK data. No formal hypothesis testing is planned. To further explore on the plasma PK data, dose proportionality will be assessed for SAD-HS and MAD-HS segments.

- Dose Proportionality
  - SAD-HS

    Dose proportionality will be assessed for C_{max}, AUC_t and $AUC_{0\text{-}inf}$ using the power model. An assessment of dose proportionality will not be based strictly on statistical rules criteria but rather, several factors will be considered when assessing dose proportionality, such as results derived from a Power Model (e.g., the slope estimate, and the width of the 90% confidence intervals [CIs]), graphical evaluation, and descriptive statistics by dose level.

    Details are as follows:

    - Power Model: The power model will be used to estimate the slope parameter and the 90% CIs for the slope. The general form of the power model is described as:

      $\ln(\text{PK Parameter}) = \beta_0 + \beta_1 \ln(\text{Dose}) + \varepsilon$

      This approach is usually referred to as a power model because after exponentiation:

      $\text{PK Parameter} = \alpha\ \text{Dose}^{\beta 1}$

      where α only depends on β_0 and ε and represents the y-intercept of the line and β_1 represents the slope of the line.

      Linear relationships between the log-transformed PK parameter and the log of the dose will be tested to obtain an estimate of the slope parameter ($\beta 1$) and 90% confidence interval (CI) for the slope. Dose proportionality can generally be concluded if the 90% CI around the slope estimate (i.e., β_1) includes the value of 1.
  - MAD-HS
    - Similar model as explained above will be used to assess dose proportionality for the parameters C_{max}, AUC_t , $AUC_{0\text{-}inf}$ and AUC_τ calculated on Day 1 and Day 7 separately.

Food Effect Analysis

- FE Segment

The effect of food will be assessed for AUC_∞, $AUC_{0\text{-}t}$, C_{max} using mixed effect model.

A mixed effect model will be fitted separately to each of the log transformed PK parameters with period and treatment (fed or fasted) as fixed effects and subject as a random effect. Model assumptions will be checked and appropriate adjustments may be applied to the data. Point estimates for the differences in means (EP547 fed – EP547 fasted) and corresponding 90% confidence intervals (CIs) will be constructed from the least-squares means, using the residual variance. These will then be back-transformed to provide point estimates and corresponding 90% CIs for the ratio of geometric means fed:fasted. Intra-subject coefficient from the model will also be presented.

The effect of food on T_{max} will be analyzed nonparametrically using the Wilcoxon signed-rank test to compute the point estimate and 90% CI for the median difference (EP547 fed – EP547 fasted). This endpoint will not be log transformed for analysis.

3.4 Multiple Comparisons and Multiplicity Adjustments.

Not applicable for this study.

3.5 Handling of Missing Data

For the classification of Treatment emergent adverse event (TEAE) and Concomitant medication, the following will be applied in the following order:

a. If all dates/times (start and stop) missing, the event/medication will automatically be classified as a TEAE/Concomitant medication.

b. For adverse events (AEs) with a missing start date/time, if the event end date/time is prior to first study drug administration, the event will not be classified as a TEAE.

c. If only the AE start year/ medication end year is present and is the same or is after the first study drug administration year unit, the event/medication will be classified as a TEAE/Concomitant medication.

d. If the AE start month and year/medication end month and year are present and are the same or after the first study drug administration month and year units, the event/medication will be classified as a TEAE/Concomitant medication.

For the PK analysis the following will be applied:

a. For the concentration descriptive summaries, concentrations may be excluded if sampling time deviation is considered large to affect the profile at the discretion of the pharmacokineticist.

b. Concentrations (plasma and skin) that are below limit of quantification (BLQ which is 10 ng/mL undiluted) prior to the first quantifiable value will be set equal to zero. Post dose BLQ concentrations will be set to missing.

c. Where there are no results (NR), these will be set to missing.

d. If more than 75% of values per nominal timepoint and treatment group are BLQ, then all descriptive statistics, except for nBLQ, will be denoted as not calculable (NC).

e. For the calculation and graphical representation (semi-log and log-log plots) of geometric descriptive statistics, 0 values will be set to missing.

f. For the purpose of calculating the non-compartmental PK parameters, plasma concentrations that are BLQ prior to the first quantifiable value will be set equal to zero. BLQ values after measurable concentrations will be set to missing.

g. For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

Conversion of categorical values

In some instances, continuous variables are expressed as a range (i.e. < 10). In such cases, values may be converted to the range boundary (upper or lower limit as applicable). As an example, a value of <10 may be converted to 10. Such substitutions will be clearly documented in the footnotes of relevant outputs.

3.6 Coding of Events and Medications

Medical history and AE verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary, version March 2020. Medications will be mapped to the full WHO-DD Anatomical Therapeutic Chemical (ATC) class hierarchy, but PTs will be of primary interest in this analysis.

3.7 Treatment Groups/Treatment Sequence

3.7.1 Baseline Characteristic, Demography, Safety and PD outputs

For listings, all segment data will be presented together in one listing as per segment and dose level (available) with the following treatment group labels:

Group 1: SAD HS/ EP547 25 mg

Group 2: SAD HS/ EP547 75 mg

Group 3: SAD HS/ EP547 225 mg

Group 4: SAD HS/ EP547 450 mg

Group 5: SAD HS/ EP547 TBD mg

Group 6: MAD HS/ EP547 25 mg QD

Group 7: MAD HS/ EP547 75 mg QD

Group 8: MAD HS/ EP547 TBD mg QD

Group 9: SD CP/ EP547 TBD mg

Group 10: SD UP/ EP547 TBD mg

Group 11: MAD CP/ EP547 TBD mg QD

Group 12: MAD CP/ EP547 TBD mg QD (optional)

Group 13: MAD UP/ EP547 TBD mg QD

Group 14: MAD UP/ EP547 TBD mg QD (optional)

For summary, separate tables will be provided for each segment (SAD-HS, MAD-HS, SD-CP/SD-UP, MAD-CP/MAD-UP) with the following treatment group labels:

SAD-HS:

EP547 25 mg (N = x)

EP547 75 mg (N = x)

EP547 225 mg (N = x)

EP547 450 mg (N = x)

EP547 TBD mg (N = x)

Overall EP547 (N = xx)

Overall Placebo (N = xx)

MAD-HS:

EP547 25 mg QD (N = x)

EP547 75 mg QD (N = x)

EP547 TBD mg QD (N = x)

Overall EP547 (N = xx)

Overall Placebo (N = xx)

SD-CP/SD-UP:

CP EP547 TBD mg (N = x)

UP EP547 TBD mg (N = x)

MAD-CP/MAD-UP:

CP EP547 TBD mg QD (N = x)

CP EP547 TBD mg QD (N = x) (optional)

UP EP547 TBD mg QD (N = x)

UP EP547 TBD mg QD (N = x) (optional)

CP Overall EP547 (N = x) (optional)

UP Overall EP547 (N = x) (optional)

CP Overall Placebo (N = x)

UP Overall Placebo (N = x)

Placebo and active treatment groups will be pooled for all descriptive analysis for healthy subject segments. For MAD/CP and MAD/UP segments, placebo and active treatment groups will be pooled only if there are multiple dose levels. Continuous and Categorical analysis will be conducted as described in section 3.1.

3.7.2 PK outputs

The same treatment group labels as mentioned in section 3.7.1 will be used for all by-participant listings.

For summary separate tables will be provided for each segment (SAD-HS, MAD-HS, SD-CP/SD-UP, MAD-CP/MAD-UP) with the following treatment group labels:

SAD-HS:

EP547 25 mg (N = x)

EP547 75 mg (N = x)

EP547 225 mg (N = x)

EP547 450 mg (N = x)

EP547 TBD mg (N = x)

MAD-HS:

EP547 25 mg QD (N = x)

EP547 TBD mg QD (N = x)

EP547 TBD mg QD (N = x)

SD-CP/SD-UP:

CP EP547 TBD mg (N = x)

UP EP547 TBD mg (N = x)

MAD-CP/MAD-UP:

CP EP547 TBD mg QD (N = x)

CP EP547 TBD mg QD (N = x) (optional)

UP EP547 TBD mg QD (N = x)

UP EP547 TBD mg QD (N = x) (optional)

Continuous analysis will be conducted as described in section 3.1.

3.7.3 Food Effect Segment

Separate tables and listings will be presented for FE segment.

All baseline, demographic, [redacted] tables will be presented by Sequence.

- Sequence 1 (N = x)
- Sequence 2 (N = x)
- Overall (N = x)

Where sequence 1 (Fasted for FE Period 1 followed by Fed for FE Period 2)
sequence 2 (Fed for FE Period 1 followed by Fasted for FE Period 2).

All safety, analysis population, and PK tables will be presented by treatment.

- EP547 75 mg Fed (N = x)
- EP547 75 mg Fasted (N = x)
- Overall (N = x) [Only for AE, CM and analysis population table]

4. ANALYSIS POPULATIONS

In this study 4 analysis sets are defined: Enrolled, Safety, Pharmacokinetic (PK), and Pharmacodynamic (PD) population.

Furthermore, any additional exploratory analysis not identified in the SAP will be included in the final CSR as exploratory post hoc analyses, including analyses for additional study populations or subgroups of interest.

4.1 Population Descriptions

4.1.1 Enrolled Population

This population will comprise all subjects who sign the informed consent form (ICF) to participate in the study, complete the screening visit procedures, and meet all eligibility criteria for enrollment.

All listings will be presented by the Enrolled Population.

4.1.2 Safety Population

This population will comprise all subjects who receive at least 1 dose of study drug, whether prematurely withdrawn from the study or not and will be based on actual treatment received.

For FE segment, Safety Population will include all randomized subjects who receive any amount of study drug (EP547 75 mg Fasted or EP547 75 mg Fed) and will be based on the actual treatment received, if this differs from what the subject was randomized to.

All safety analyses will be based on the Safety Population.

4.1.3 Pharmacokinetic (PK) Population

Plasma PK population:

Non FE segments: This population will comprise all subjects who receive at least one dose of study drug (EP547) and have any measurable plasma concentrations of EP547 and had no important protocol deviations affecting the pharmacokinetics of EP547 and for whom a sufficient number of samples are available to determine at least one PK parameter among C_{max}, T_{max} and AUC_{0-t}. Subjects will be assessed on a subject-by-subject basis for inclusion in the PK Population and will be determined by the study and sponsor pharmacokineticist. The PK Population determination will be made before unblinding post database lock.

The PK analyses for EP547 and its metabolites (as applicable) will be conducted based on the PK Population for plasma concentration data.

For FE segment: This population will include all randomized subjects who receive at least one dose of study drug (EP547 75 mg Fasted or EP547 75 mg Fed) who had no important protocol deviations affecting the PK variables of EP547 and for whom a sufficient number of samples are available to determine at least 1 PK parameter among AUC_{0-t}, C_{max} or T_{max}. All PK analysis will be based on this population. Subjects will be assessed on a subject-by-subject basis for inclusion in the PK Population and will be determined by the study and sponsor pharmacokineticist.

Urine PK population:

This population will comprise all subjects who receive at least one dose of study drug (EP547) and have any measurable urine concentrations of EP547 and had no important protocol deviations. The urine PK population determination will be made on subject-by-subject basis by the study and sponsor pharmacokineticist before unblinding post database lock.

The PK analyses for urine concentrations and parameters will be conducted based on the urine PK Population.

Skin PK population:

This population will comprise all subjects who receive at least one dose of study drug (EP547) and have any measurable skin concentrations of EP547 and had no important protocol deviations. The summary skin concentrations data of EP547 and its metabolites (as applicable) will be based on the PK population for skin concentration data.

The PK analyses for skin concentrations will be conducted based on the PK Population for skin concentration data.

4.1.4 Pharmacodynamic (PD) Population

This population will comprise all subjects belonging to the Safety Population without major protocol deviations.

The PD analyses will be conducted based on the PD Population.

5. PARTICIPANT DISPOSITION AND ANALYSIS POPULATIONS

Participant disposition and analysis population analyses will be based on the Safety and Enrolled population respectively. Participant disposition and analysis populations will be summarized descriptively as described in section 3.1 (categorical descriptive analysis). The screen failure including reason for screen failure will be presented in the by-participant data listings and will be summarized descriptively as described in section 3.1 (categorical descriptive analysis).

5.1.1 Participant Disposition

Participant disposition will include the number of participants who completed the study treatment as planned and completed the post-treatment follow-up, participants withdrawn from the study treatment and from post-treatment follow-up, as well as the primary reason for treatment termination and post-treatment follow-up termination. Participant disposition will be summarized descriptively.

5.1.2 Analysis Populations

The number of participants included in each study populations will be summarized descriptively.

In addition, the inclusion of each participant into/from each of the defined analysis populations will be presented in the by-participant data listings.

6. PROTOCOL DEVIATIONS

Protocol deviations will be presented for each participant in the by-participant data listings and the classification and important protocol deviation will be summarized descriptively as described in section 3.1 (categorical descriptive analysis) under the Safety Population.

Prior to database lock, all protocol deviations will be tracked in the Novotech Clinical Trial Management System (CTMS). All important deviations are documented on an Important Protocol Deviation (IPD) form and are reviewed and approved by Novotech medical monitor and sponsor.

Protocol deviations and important protocol deviations will be categorized as noted in the protocol deviation management plan version 1.0 dated 2020-08-25.

7. DEMOGRAPHIC AND BASELINE INFORMATION

Demographic and baseline information analysis will be based on the Safety Population. If there is a difference from the Safety Population, demographic and baseline information analysis will be repeated for the PK and PD population.

Demographic and baseline information will be summarized descriptively as described in section 3.1.

7.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics parameters will be analyzed:

Continuous descriptive analysis:

- Age (years)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2) = weight (kg) / [height (m)]2
- Estimated Glomerular Filtration Rate (eGFR) (only for UP segments)
- Child-Pugh Score (only for CP segments)

Categorical descriptive analysis:

- Sex
- Race
- Ethnicity
- eGFR (only for UP segments): G1 (≥90), G2 (60 to 89), G3a (45 to 59), G3b (30 to 44), G4 (15 to 29), and G5 (<15)
- Child-Pugh Score (only for CP segments): Class A (5 to 6 points), Class B (7 to 9 points), Class C (10 to 15 points)

Baseline eGFR will be derived using the CKD-EPI equation (Levey 2009)

$eGFR=141 \times \min(SCr/\kappa,1)^{\alpha} \times \max(SCr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x1.159 [if Black]

where

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m2

SCr (standardized serum creatinine) = mg/dL

$\kappa = 0.7$ (females) or 0.9 (males)

$\alpha = -0.329$ (females) or -0.411 (males)

min = indicates the minimum of SCr/κ or 1

max = indicates the maximum of SCr/κ or 1

age = years

7.2 Medical history

Medical history will be coded using MedDRA® and will be presented in the by-participant data listings.

Summary tables will include the number of participants (%) experiencing an event and the number of events. Participants will be counted only once for each SOC and PT level (categorical descriptive analysis).

7.3 Disease History

Disease history will be presented for SD-CP, SD-UP, MAD-CP and MAD-UP participants in the by-participant data listings. Summary tables will include the number of participants (%) experiencing each disease including liver disease, end stage renal disease, pruritus, suicidal indentaions and so on (categorical descriptive analysis).

7.4 Hemodialysis History

Hemodialysis history will be presented for SD-UP and MAD-UP participants in the by-participant data listings.

The following parameters will be summarized:

Continuous descriptive analysis:

- Years required for chronic hemodialysis
- Years using current hemodialysis procedure
- Times a week that the patient undergoes hemodialysis
- Hemodialysis undergone per week
- Hours taken for hemodialysis procedure
- The dialysate - Sodium/Na (meq/L)
- The dialysate - Potassium/K (meq/L)
- The dialysate - Calcium/Ca (meq/L)
- The dialysate - Magnesium/Mg (meq/L)
- The dialysate - Bicarbonate/HC03 (meq/L)
- The dialysate - Chloride/Cl (meq/L)
- The dialysate - Acetate (meq/L)
- The dialysate - Glucose (mg/dL)
- Dry weight
- Dialysis adequacy measurement (Kt/V and/or URR)

Categorical descriptive analysis:

- Residual renal function
- Type of hemodialysis
- Procedure membrane
- Type of heparin

7.5 Itch History

Itch history will be presented for MAD-CP and MAD-UP participants only in the by-participant data listings.

The following parameters will be summarized:

Categorical descriptive analysis:

- Number of patients having significant or consistent itch prior to liver/kidney disease diagnosis
- Time when itch is worse
- Does itching interfere patient’s sleep

- Areas of body which are itchy
- Any secondary lesions to scratching ?
- Is itch more prominent in different seasons ?
- Seasons in which itch are worse
- Circumstance that aggravate itching
- Has UV light been used for itching

7.6 Drug Screening and other Screening laboratory

Drug Screening and other Screening laboratory including Hepatitis B Surface Antigen (HBsAg), Hepatitis C Antibody (HCVAb), Human Immunodeficiency Virus (HIV-1/HIV-2), urine drug test, Cotinine test, alcohol test, coagulation (including INR, APTT, PT), pregnancy test, and follicle-stimulating hormone (FSH) results will be presented in the by-participant data listings and will be summarized descriptively as described in section 3.1 (categorical descriptive analysis and continuous descriptive analysis) under the Safety Population.

7.7 Inclusion/Exclusion Criteria Exceptions and Eligibility Criteria

The subject eligibility responses as well as the violation of specific inclusion/exclusion criteria will be summarized descriptively and also presented in the by-subject data listings.

8. TREATMENT EXPOSURE

All study drug administration information (study drug administered (Yes/No), reason not administered, number of capsules taken, and date and time of administration will be presented in the by-participant data listings under the Safety Population.

Treatment exposure in duration and the number of capsules will be summarized descriptively as described in section 3.1 under the Safety population.

- The Treatment Exposure (duration in days) is defined as:

  Date of Last Study Drug Administration - Date of First Study Drug Administration + 1.

9. PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class Level 2 and PT as noted in section 3.1 (categorical descriptive analysis). Participant who used the same medication on multiple occasions will only be counted once in the specific category (PT). PTs will be sorted alphabetically. In addition to the summaries by the coded terms, the number of participants who used at least one concomitant medication during the study will be presented under the Safety Population.

Prior medications and Concomitant medications will be presented in the by-participant data listings under the Enrolled Population.

10. PHARMACOKINETICS

10.1 Plasma PK Analysis

All PK summary tables will be based on the PK Population for plasma concentration data. All analyses will be summarized as described in section 3.1 (PK - continuous descriptive analysis). All listings will be based on the PK Population.

The following pharmacokinetic parameters will, where possible, be determined from the plasma concentrations of EP547 (and its metabolites if applicable) by non-compartmental method using Phoenix WinNonlin software (Version 8.1 or higher):

Plasma Pharmacokinetic Parameters at non-steady state on Day 1 following single dose administration for SAD (SD) and MAD segments:

Parameter	Definition
C_{max}	Maximum concentration which is directly determined from the plasma concentration time profiles
T_{max}	Time to maximum concentration. If the same C_{max} concentration occurs at different time points, T_{max} is assigned to the first occurrence of C_{max}.
AUC_{0-t}	Area under the drug concentration-time curve, from time zero to the last measurable concentration using the 'Linear Up and Log Down' method
AUC_{0-24hr}	Area under the drug concentration-time curve, from time zero (time of dosing) to 24 hours post-dose using the 'linear Up and Log Down' method
AUC_{0-48hr}	Area under the drug concentration-time curve, from time zero (time of dosing) to 48 hours post-dose using the 'linear Up and Log Down' method (only for SAD cohort)

$AUC_{0\text{-inf}}$	Area under the drug concentration-time curve, from time zero to infinity (∞) using the following formula $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t^{'}}{\lambda_z}$ Where, $C_t^{'}$ is the observed concentration at the time t (last time point with a measurable plasma concentration above the quantification limit) at which quantification was still possible, the calculation of λ_z or k_{el} is given below.
$AUC_{\%extrap}$	The percentage of the AUC that has been extrapolated beyond the last observed data point, using the following formula $AUC_{\%extrap} = \left(\frac{AUC_{0-\infty} - AUC_{0-t}}{AUC_{0-\infty}}\right) * 100$
λ_z or k_{el}	The apparent terminal elimination rate constant, will be estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles.
$t_{½}$	Apparent terminal half-life, using the following formula $T_{1/2} = \frac{Ln(2)}{\lambda_z}$
CL/F	Apparent total plasma clearance, using the following formula $CL/F = \frac{D}{AUC_{0-\infty}}$ Where D = Administered dose; $AUC_{0-\infty} = AUC_{0\text{-inf}}$
V_z/F	Apparent terminal volume of distribution, using the following formula $V_z/F = \frac{CL/F}{\lambda_z}\ Or\ \frac{Dose}{\lambda_z \times AUC_{inf}}$
Corrected M/P ratio for C_{max}	Corrected metabolite to parent ratio for C_{max} is calculated using the following formulae (C_{max} metabolite/C_{max} parent) *(Molecular Weight of parent drug/Molecular Weight of metabolite)
Corrected M/P ratio for $AUC_{0\text{-t}}$	Corrected metabolite to parent ratio for $AUC_{0\text{-t}}$ is calculated using the following formulae ($AUC_{0\text{-t}}$ metabolite/ $AUC_{0\text{-t}}$ parent) *(Molecular Weight of parent drug/Molecular Weight of metabolite)

Plasma Pharmacokinetic Parameters at steady state on pre-defined days following multiple dose administration for the MAD-HS and MAD-CP segments (Day 1 and Day 7) and for the MAD-UP segment (Day 1, Day 2, Day 6, and Day 7)

Parameter	Definition
C_{max}	Maximum steady state concentration time over the dosing interval
C_{trough}	The pre-dose trough concentration observed at the last planned timepoint prior to next dosing
T_{max}	Time to reach maximum concentration over the dosing interval. If the same C_{max} concentration occurs at different time points, T_{max} is assigned to the first occurrence of C_{max}.
AUC_{0-t}	Area under the drug concentration-time curve, from time zero to the last measurable concentration using the 'Linear Up and Log Down' method
$AUC_{0-\tau}$	Area under the plasma concentration-time curve over a dosing interval using the 'Linear Up and Log Down' method
AUC_{0-24hr}	Area under the drug concentration-time curve, from time zero (time of dosing) to 24 hours post-dose using the 'linear Up and Log Down' method
AUC_{0-48hr}	Area under the drug concentration-time curve, from time zero (time of dosing) to 48 hours post-dose using the 'linear Up and Log Down' method
λ_z or k_{el}	The apparent terminal elimination rate constant, will be estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles.
$t_{½}$	Apparent terminal half-life, using the following formula $T_{1/2} = \frac{Ln(2)}{\lambda_z}$
CL/F_{ss}	Apparent total plasma clearance, using the following formula $CL/F_{ss} = Dose/ AUC_{0-\tau}$
V_z/F_{ss}	Apparent terminal volume of distribution, using the following formula $Vz/F_{ss} = (Dose)/ (\lambda_z . AUC_{0-\tau})$
R_{auc}	Accumulation ratio based on AUC, calculated as $AUC_{0-\tau}$ at steady state divided by $AUC_{0-\tau}$ after a single day
R_{cmax}	Accumulation ratio based on C_{max}, calculated as C_{max} at steady state divided by C_{max} after a single day
Corrected M/P ratio for C_{max}	Corrected metabolite to parent ratio for C_{max} is calculated using the following formula

	(C_{max} metabolite/C_{max} parent) *(Molecular Weight of parent drug/Molecular Weight of metabolite)
Corrected M/P ratio for AUC_{0-t}	Corrected metabolite to parent ratio for AUC_{0-t} is calculated using the following formula (AUC_{0-t} metabolite/ AUC_{0-t} parent) *(Molecular Weight of parent drug/Molecular Weight of metabolite)

Plasma Pharmacokinetic Parameters on Day 1 (Period 1 & Period 2) for FE segment:

Parameter	Definition
C_{max}	Maximum concentration which is directly determined from the plasma concentration time profiles
T_{max}	Time to maximum concentration. If the same C_{max} concentration occurs at different time points, T_{max} is assigned to the first occurrence of C_{max}.
AUC_{0-t}	Area under the drug concentration-time curve, from time zero to the last measurable concentration using the 'Linear Up and Log Down' method
AUC_{0-inf}	Area under the drug concentration-time curve, from time zero to infinity (∞) using the following formula $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t^{'}}{\lambda_z}$ Where, $C_t^{'}$ is the observed concentration at the time t (last time point with a measurable plasma concentration above the quantification limit) at which quantification was still possible, the calculation of λ_z or k_{el} is given below.
$AUC_{\%extrap}$	The percentage of the AUC that has been extrapolated beyond the last observed data point, using the following formula $AUC_{\%extrap} = \left(\frac{AUC_{0-\infty} - AUC_{0-t}}{AUC_{0-\infty}}\right) * 100$
λ_z or k_{el}	The apparent terminal elimination rate constant, will be estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles.
$t_{1/2}$	Apparent terminal half-life, using the following formula $T_{1/2} = \frac{Ln(2)}{\lambda_z}$.
T_{lag}	T_{lag} signifies the delay between the time of dosing and time of appearance of concentration in the sampling compartment
CL/F	Apparent total plasma clearance, using the following formula $CL/F = \frac{D}{AUC_{0-\infty}}$ Where D = Administered dose; $AUC_{0-\infty} = AUC_{0-inf}$
V_z/F	Apparent terminal volume of distribution, using the following formula $V_z/F = \frac{CL/F}{\lambda_z}\ Or\ \frac{Dose}{\lambda_z \times AUC_{inf}}$
Corrected M/P ratio for C_{max}	Corrected metabolite to parent ratio for C_{max} is calculated using the following formula (C_{max} metabolite/C_{max} parent) *(Molecular Weight of parent drug/Molecular Weight of metabolite)

Corrected M/P ratio for AUC_{0-t}	Corrected metabolite to parent ratio for AUC_{0-t} is calculated using the following formula (AUC_{0-t} metabolite/ AUC_{0-t} parent) *(Molecular Weight of parent drug/Molecular Weight of metabolite)

If the pre-dose concentration following first dose administration is ≤ 5% of the C_{max} value, the participant's data will be included in both pharmacokinetic and statistical analysis without any adjustment. If the pre-dose value is > 5% of C_{max}, the subject will be dropped from both pharmacokinetic and statistical analysis.

Additional pharmacokinetic parameters may be determined where appropriate.

Corrected metabolite to parent ratio will be calculated for C_{max} and AUC_{0-t} for steady state and non-steady state dosing profiles of HS segments (SAD & MAD). [redacted]

Pharmacokinetic analysis will be carried out using actual doses and blood sampling times, where possible. If actual times are missing, nominal times may be used with sponsor approval.

Plasma concentrations of EP547 (and its metabolites if applicable) will be used as supplied by the bioanalytical laboratory. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the bioanalytical laboratory.

10.1.1 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life and AUC

10.1.1.1 Number of Data Points

- In order for regression analysis to be performed, at least 3 data points will be included in the regression analysis and not including C_{max}.

10.1.1.2 Goodness of Fit

- If data permits, the default 'best fit' method by Phoenix WinNonlin will be used for the selection of slopes to determine 'λz'. If data do not permit, then the slope selection will be done by visual inspection or by a manual method to determine λz.
- When assessing terminal elimination phases, the adjusted R^2 value will be used as a measure of the goodness of fit of the data points to the determined line.
- Regression-based parameters (λ_z, AUC_{0-inf}, $t_{1/2}$, CL/F or CL/Fss, and V_z/F or V_z/Fss) will only be calculated if the adjusted R^2 value of the regression line is greater than or equal to 0.8 and $AUC_{\%extrap}$ is <20%. If regression-based parameters cannot be calculated, they will be set to "NC", defined as "not calculable" in the data listings and summary tables as appropriate.

10.1.1.3 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.
- All AUC values will be calculated using the 'linear up / log down' trapezoidal rule where the linear trapezoidal rule will be used for increasing concentrations and the log trapezoidal rule for decreasing concentrations.

10.2 Urine PK Analysis (SAD-HS only)

All PK summary tables will be based on the Urine PK Population for concentration data. All analyses will be summarized as described in section 3.1 (PK - continuous descriptive analysis). All listings will be based on the Enrolled Population. All missing and BLQ handling of urine concentrations for PK analysis will be based on section 3.5.

For SAD-HS, the urinary output will be collected during the intervals -6-0 predose, and 0-6, 6-12, 12-18 hours post dose on Day 1, 18-24, 24-30, 30-36 hours post dose on Day 2, 36-42, 42-48 hours post dose on Day 3.

The following urine pharmacokinetic parameters of EP547 (and its metabolites if applicable) will, where possible, be determined from the urine collection volume and concentrations of the analyte(s) by non-compartmental method using Phoenix WinNonlin software (Version 8.1 or higher):

Parameter	Definition
$Ae_{t1\text{-}t2}$	Total amount of the analyte excreted in urine from time t1 to t2 hours (for each urine time interval) $Ae_{t1-t2} = Cu_{t1-t2} \times Vu_{t1-t2}$, where Vu = the volume of urine collected and Cu = the concentration of urine in each collection interval sample
CAe	Cumulative amount excreted in urine considering time 0 to 48 hours. $CAe = Cu_{0-48} \times Vu_{0-48}$
$Fe_{t1\text{-}t2}$	Fraction of the administered dose the analyte excreted into the urine from time t1 to t2 hours (for each urine time interval) $Fe_{t1-t2} = \left(\frac{Ae_{t1-t2}(mg)}{Dose(mg)}\right) \times 100$
CFe	Cumulative fraction of the administered dose the analyte excreted into the urine considering time 0 to 48 hours. $Fe_{0-48} = \left(\frac{Ae_{0-48}(mg)}{Dose(mg)}\right) \times 100$
CLr	Renal clearance calculated as CLr = Cumulative Ae/Plasma $AUC_{0\text{-}48}$
Corrected Urine Fe for metabolite	(Fe metabolite in urine) * (Molecular Weight of parent drug/ Molecular Weight of metabolite)
Corrected Urine Ae for metabolite	(Ae metabolite in urine) *(Molecular Weight of parent drug/ Molecular Weight of metabolite)

The additional parameters for urine Corrected Fe & Corrected Ae for metabolite will be derived for SAD-HS for each urine sample interval.(ie; Fe (0-6hr), Fe(6-12 hr), Fe(12-18 hr) etc..).

PK concentration and parameter data will be analyzed descriptively as noted in section 3.1.

10.3 Skin PK Analysis

All PK summary tables will be based on the PK Population for skin concentration data. All skin concentrations will be summarized as described in section 3.1 (PK - continuous descriptive analysis). A listing will be provided for the same based on the Enrolled Population.

For last dose level for MAD-HS and all dose levels for MAD-CP and MAD-UP, Skin EP547 and metabolites (as applicable) concentrations will be summarized.

10.4 Pharmacokinetic Noncompartmental Analysis (NCA)

10.4.1 General Plasma NCA Pharmacokinetic Settings

The general settings in Phoenix WinNonlin® for generation of plasma PK parameters are as listed below.

- NCA Model Type Plasma (200-202)
- Weighting Uniform
- AUC Calculation Method: Linear Up/Log Down
- Dose Options Type Extravascular
- Slopes Setting Fit Method: Best Fit
- Rsq_Adjusted Criteria for 'λz' 0.8
- AUC% extrapolation Criteria 20

10.4.2 General Urine NCA Pharmacokinetic Settings

The general settings in Phoenix WinNonlin® for generation of urine PK parameters are as listed below.

- NCA Model Type: Urine (210-212)
- Weighting: Uniform
- AUC Calculation Method (if applicable): Linear Up/Log Down

10.4.3 Inferential Analyses

For SAD-HS and MAD-HS, the following endpoints will be analyzed as described in section 3.3:

- Dose proportionality:
  - C_{trough} (Only Day 7 value to be used to assess DP for MAD)
  - C_{max}
  - AUC_{0-t}
  - AUC_{0-inf}
  - $AUC_{0-\tau}$ (as appropriate, MAD only)

Dose proportionality will be assessed graphically (Cmax, AUC_{0-t} and AUC_{0-inf} versus dose) on log scale for both axes. PK parameters derived from Day 1 (SAD & MAD) and Day 7 (MAD) will be subjected to dose proportionality assessment for entire dose range studied for EP-547-101. From each model, the slope of the regression line β will be presented along with the 90% CI of the slope. The regression line formulae along with correlation coefficient (r^2) will be presented in the plot.

Sample SAS Code for dose-proportionality analysis using power model. Programmers will need to modify as appropriate to the study:

```
proc mixed;
   by PKParameter;
    model lnPKParameter = lnDose / cl alpha=0.1 solution ddfm=kr;
run;
```

For FE-HS, the following endpoints will be analyzed as described in section 3.3:

- Food Effect analysis:
  - C_{max}
  - AUC_{0-t}
  - AUC_{0-inf}
  - T_{max}

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

11.1 [redacted]

[redacted]

11.2 [redacted]

[redacted]

11.3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.7 [redacted]

[redacted]

12. EFFICACY

No efficacy analysis is planned for this study.

13. SAFETY

Safety endpoints will be analyzed using the Safety Population. Safety endpoints will be summarized descriptively as described in section 3.1.

13.1 Adverse Events

AEs will be coded using MedDRA. All AE summaries will be restricted to TEAEs only. Summary tables will include the number of participants (%) experiencing an event and the number of events. Participants will be counted only once for each SOC and PT level (categorical descriptive analysis).

The TEAE summaries will include:

- Overall summary of TEAEs.
- TEAE summary by SOC and PT.
- TEAE summary of serious events by SOC and PT.
- Drug Related TEAEs summary by SOC and PT.
- TEAE summary by SOC, PT and Maximum Severity.
- TEAE summary of events leading to study treatment withdrawal by SOC and PT.

All AEs will be listed and will include verbatim term, PT, SOC, serious adverse event (SAE), TEAE, severity, outcome, actions taken with study treatment, relationship with study treatment and discontinuation from the study. Separate listings will be created for SAEs, Drug-related AE, AEs leading to discontinuation of study drug, and AEs resulting in death. These listings will be presented by treatment group (grouping provided in section 3.7) sorted by subject ID and AE start date.

13.2 Safety Laboratory Assessments

Blood and urine samples will be collected at the time points specified in the Schedule of Events (refer to the Protocol) to conduct hematology/coagulation, chemistry and urinalysis (including microscopic examinations) analyses.

The following tests will be performed within each of the specified test panels:

Hematology:

- Basophils
- Eosinophils
- Hematocrit
- Hemoglobin
- Lymphocytes
- Monocytes
- MPV
- Neutrophils
- Platelets
- Red blood cells (erythrocytes) (RBC)
- White blood cells (leukocytes) (WBC) (total and differential)

Chemistry:

- Albumin
- Alkaline Phosphatase (ALP)

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Bicarbonate
- Bile acids
- Blood Urea Nitrogen (BUN)
- Corrected Calcium
- Calcium
- Chloride
- Creatinine
- Creatine phosphokinase (CPK)
- Direct Bilirubin
- Gamma-glutamyltransferase (GGT)
- High-Density Lipoprotein cholesterol (HDL-c)
- Lactate Dehydrogenase (LDH)
- Low-Density Lipoprotein cholesterol (LDL-c)
- Magnesium
- Phosphate
- Potassium
- Sodium
- Triglycerides
- Total Bilirubin
- Total Cholesterol
- Total Protein
- Urea

Urinalysis (Dipstick) & Microscopic Urinalysis:

- Bilirubin
- Blood
- Color
- Glucose
- Ketones
- Leukocytes
- Nitrite
- pH
- Protein
- Specific Gravity
- Urobilinogen

- Microscopic Examinations (listing only)

All laboratory data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

Results for individual parameters may be reported in different units depending on the analyzing laboratory. If required, the results (and the corresponding normal range cut-off values) for individual parameters may be converted to International System of Units (S.I.) to summarize the data. Parameters will be presented in both units (S.I and conventional units) in the listing.

For all the parameters where a unit value has been reported, the parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Albumin (g/L)'. For the urinalysis parameters, the parameter name will be the reported test name only. Parameters will be sorted alphabetically within tables and listings.

For all parameters where a normal range limit value was reported, the normal range will be derived based on the available lower and upper limit values and any reported mathematical symbols. If both a lower and upper limit value is available, the normal range will be presented as '(Lower, Upper)'.

The reported results for each parameter with a defined normal range will be classified ('Low', 'Normal', 'High') in relation to the defined normal range limits. If a result is equal to the normal range cut-off value, the result will be considered 'Normal'.

The hematology, chemistry and urinalysis results tables will present summary statistics for each laboratory parameter within the specific test panel. For each parameter, summaries will be presented for the baseline and each scheduled post-baseline visit. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis).

The decimal precision to which the summaries for each parameter will be based on the maximum number of decimals to which the reported result or the normal range limits are presented to in the raw data. The results and normal ranges will be displayed to the same decimal precision in the listings.

The hematology and chemistry result with values out of normal range will present counts and percentages for the reported results at baseline and each post-baseline visit/time point. Result categories will be ordered as 'Low', 'Normal' and 'High' (categorical descriptive analysis).

Additionally, counts (%) of number participants with normal and abnormal CS/NCS at each scheduled time point will also be presented along with shift tables that will represent the changes in normal categories across post-baseline time points (categorical descriptive analysis).

13.3 Vital Signs

The following vital signs measurements will be taken at the time points specified in the Schedule of Events (refer to the Protocol):

- Pulse Rate (beats/min)
- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Respiratory rate (breaths/min)
- Temperature (ºC)
- Oxygen Saturation (%)
- Body Weight (kg)

All vital signs data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Systolic Blood Pressure (mmHg)'. Parameters will be sorted in the order that the measurements were collected in on the Vital Signs eCRF page within the tables and listings.

Vital signs measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis).

The decimal precision to which the summaries for each parameter will presented will be based on the maximum number of decimals to which the results were reported on the eCRF.

13.4 12-Lead Electrocardiogram (ECG)

The following ECG measurements will be taken at the time points specified in the Schedule of Events (refer to the Protocol):

- Ventricular Rate (beats/min)
- PR Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- QRS Duration (msec)
- Overall Clinical Interpretation Finding

All ECG data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Ventricular Rate (beats/min)'. Parameters will be sorted in the order that the measurements were collected in on the ECG eCRF page within the tables and listings.

ECG measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis).

The decimal precision for each parameter will be based on the maximum number of decimals to which the results were reported on the eCRF.

The summary of overall ECG interpretation findings table will present counts and percentages along with shift tables that will represent the changes in normal and abnormal NCS/CS categories across post-baseline time points (categorical descriptive analysis).

13.5 Physical Examinations

By-participant data listings will be created for all physical examination parameters and all time points.

13.6 Hemodialysis

Hemodialysis will be presented for SD-UP and MAD-UP participants in the by-participant data listings.

The following hemodialysis measurements will be taken at the time points specified in the Schedule of Events (refer to the Protocol) and will be summarized descriptively as described in section 3.1 (categorical descriptive analysis and continuous descriptive analysis) under the Safety Population.

<u>Continuous descriptive analysis:</u>

- The dialysate - Sodium/Na (meq/L)
- The dialysate - Potassium/K (meq/L)
- The dialysate - Calcium/Ca (meq/L)
- The dialysate - Magnesium/Mg (meq/L)
- The dialysate - Bicarbonate/HC03 (meq/L)
- The dialysate - Chloride/Cl (meq/L)

- The dialysate - Acetate (meq/L)
- The dialysate - Glucose (mg/dL)
- Ultrafiltration volume (kg)
- Dialysis adequacy measurement (Kt/V and/or URR)

Categorical descriptive analysis:

- Type of hemodialysis
- Procedure membrane
- Type of heparin

14. IMMUNOGENICITY

No immunogenicity analysis is planned for this study.

15. CHANGES TO THE PLANNED ANALYSIS

Not applicable.

16. INTERIM AND FINAL ANALYSIS

16.1 Interim Analysis

An interim analysis may be performed at Sponsor's discretion for internal decision making and use the data towards Investigational New Drug (IND). Additional data analyses may also be performed during the study in the event that the Sponsor and Investigators determine that there is a need for further evaluation of the data.

An unblinded interim analysis is planned once all SAD-HS and MAD-HS subjects have completed the study. For these subjects, safety and tolerability together with PK and PD data will be examined as a preliminary evaluation of safety and tolerability, PK and PD. The interim analysis will only be conducted on SAD-HS and MAD-HS subjects and the results derived out of this interim analysis will only be used for internal purposes and may not result in any change to the study protocol. The data for SAD-HS and MAD-HS will be frozen prior to the interim analysis thereby having it unblinded to Sponsor as well as Novotech.

16.2 Final Analysis (End of Study)

The final analysis will be conducted after all participants have completed the study, the clinical database has been locked, the analysis populations have been approved and the study has been unblinded.

The final analysis will be based on the SAP and include data from all segments. Any deviations from the planned analysis will be documented in the CSR.

17. SOFTWARE

- SAS® Version 9.2 or higher (SAS Institute, Cary, North Carolina, USA).
- Phoenix WinNonlin® (Certara, USA) Version 8.1 or higher.

18. TABLES

Table Number	Table Title	Population	Interim	Final
14.1	**Demographics and Other Baseline Characteristics**			
14.1.1a	Analysis Population – SAD-HS	Enrolled	×	×
14.1.1b	Analysis Population – MAD-HS	Enrolled	×	×
14.1.1c	Analysis Population – SD-CP/SD-UP	Enrolled		×
14.1.1d	Analysis Population – MAD-CP/MAD-UP	Enrolled		×
14.1.1e	Analysis Population – FE-HS	Enrolled		
14.1.2a	Inclusion/Exclusion Criteria – SAD-HS	All Subjects	×	×
14.1.2b	Inclusion/Exclusion Criteria – MAD-HS	All Subjects	×	×
14.1.2c	Inclusion/Exclusion Criteria – SD-CP/SD-UP	All Subjects		×
14.1.2d	Inclusion/Exclusion Criteria – MAD-CP/MAD-UP	All Subjects		×
14.1.2e	Inclusion/Exclusion Criteria – FE-HS	All Subjects		
14.1.3a	Subject Disposition – SAD-HS	Safety	×	×
14.1.3b	Subject Disposition – MAD-HS	Safety	×	×
14.1.3c	Subject Disposition – SD-CP/SD-UP	Safety		×
14.1.3d	Subject Disposition – MAD-CP/MAD-UP	Safety		×
14.1.3e	Subject Disposition – FE-HS	Safety		
14.1.4	Screen Failures	All Subjects	×	×
14.1.5a	Protocol Deviations – SAD-HS	Safety	×	×
14.1.5b	Protocol Deviations – MAD-HS	Safety	×	×
14.1.5c	Protocol Deviations – SD-CP/SD-UP	Safety		×
14.1.5d	Protocol Deviations – MAD-CP/MAD-UP	Safety		×
14.1.5e	Protocol Deviations – FE-HS	Safety		
14.1.6.1a	Demographics and Baseline Characteristics – SAD-HS	Safety	×	×
14.1.6.1b	Demographics and Baseline Characteristics – MAD-HS	Safety	×	×
14.1.6.1c	Demographics and Baseline Characteristics – SD-CP/SD-UP	Safety		×
14.1.6.1d	Demographics and Baseline Characteristics – MAD-CP/MAD-UP	Safety		×
14.1.6.1e	Demographics and Baseline Characteristics – FE-HS	Safety		
14.1.6.2a	Demographics and Baseline Characteristics – SAD-HS	PK	×	×
14.1.6.2b	Demographics and Baseline Characteristics – MAD-HS	PK	×	×
14.1.6.2c	Demographics and Baseline Characteristics – SD-CP/SD-UP	PK		×

Table Number	Table Title	Population	Interim	Final
14.1.6.2d	Demographics and Baseline Characteristics – MAD-CP/MAD-UP	PK		×
14.1.6.2e	Demographics and Baseline Characteristics – FE-HS	PK		
14.1.6.3a	Demographics and Baseline Characteristics – SAD-HS	PD	×	×
14.1.6.3b	Demographics and Baseline Characteristics – MAD-HS	PD	×	×
14.1.6.3c	Demographics and Baseline Characteristics – SD-CP/SD-UP	PD		×
14.1.6.3d	Demographics and Baseline Characteristics – MAD-CP/MAD-UP	PD		×
14.1.6.3e	Demographics and Baseline Characteristics – FE-HS	PD		
14.1.7a	Medical History – SAD-HS	Safety	×	×
14.1.7b	Medical History – MAD-HS	Safety	×	×
14.1.7c	Medical History – SD-CP/SD-UP	Safety		×
14.1.7d	Medical History – MAD-CP/MAD-UP	Safety		×
14.1.7e	Medical History – FE-HS	Safety		
14.1.8c	Disease History – SD-CP/SD-UP	Safety		×
14.1.8d	Disease History – MAD-CP/MAD-UP	Safety		×
14.1.9c	Hemodialysis History – SD-UP	Safety		×
14.1.9d	Hemodialysis History – MAD-UP	Safety		×
14.1.10d	Itch History – MAD-CP/MAD-UP	Safety		×
14.1.11a	Drug Screening and Other Screening Laboratory Results – SAD-HS	Safety	×	×
14.1.11b	Drug Screening and Other Screening Laboratory Results - MAD-HS	Safety	×	×
14.1.11c	Drug Screening and Other Screening Laboratory Results - SD-CP/SD-UP	Safety		×
14.1.11d	Drug Screening and Other Screening Laboratory Results - MAD-CP/MAD-UP	Safety		×
14.1.11e	Drug Screening and Other Screening Laboratory Results – FE-HS	Safety		
14.1.12a	Study Drug Administration – SAD-HS	Safety	×	×
14.1.12b	Study Drug Administration – MAD-HS	Safety	×	×
14.1.12c	Study Drug Administration – SD-CP/SD-UP	Safety		×
14.1.12d	Study Drug Administration – MAD-CP/MAD-UP	Safety		×

Table Number	Table Title	Population	Interim	Final
14.1.12e	Study Drug Administration – FE-HS	Safety		
14.2	**Efficacy/PK/PD**			
14.2.1a	Plasma EP547 & EP3583 Concentrations by Treatment and Time – SAD-HS	PK	×	×
14.2.1b	Plasma EP547 & EP3583 Concentrations by Treatment and Time – MAD-HS	PK	×	×
14.2.1c	Plasma EP547 & EP3583 Concentrations by Treatment and Time – SD-CP/SD-UP	PK		×
14.2.1d	Plasma EP547 & EP3583 Concentrations by Treatment and Time – MAD-CP/MAD-UP	PK		×
14.2.1e	Plasma EP547 Concentrations by Treatment and Time – FE-HS	PK		
14.2.2a	Plasma EP547 & EP3583 Pharmacokinetic Parameters by Treatment – SAD-HS	PK	×	×
14.2.2b	Plasma EP547 & EP3583 Pharmacokinetic Parameters by Treatment – MAD-HS	PK	×	×
14.2.2c	Plasma EP547 & EP3583 Pharmacokinetic Parameters by Treatment – SD-CP/SD-UP	PK		×
14.2.2d	Plasma EP547 & EP3583 Pharmacokinetic Parameters by Treatment – MAD-CP/MAD-UP	PK		×
14.2.2e	Plasma EP547 Pharmacokinetic Parameters by Treatment – FE-HS	PK		
14.2.3.1a	Urine EP547 and EP3583 Concentrations by Treatment and Time – SAD-HS	Urine PK	×	×
14.2.3.2a	Urine EP547 and EP3538 Pharmacokinetic Parameters by Treatment – SAD-HS	Urine PK	×	×
14.2.4a	Plasma EP547 Dose Proportionality – SAD-HS	PK	×	×
14.2.4b	Plasma EP547 Dose Proportionality – MAD-HS	PK	×	×
14.2.4e	Analysis of Food Effect – FE-HS	PK		
14.2.5b	Skin EP547 & EP3583 Concentration by Treatment and Time – MAD-HS	Skin PK	×	×

Table Number	Table Title	Population	Interim	Final
14.2.5d	Skin EP547 & EP3583 Concentration by Treatment and Time – MAD-CP/MAD-UP	Skin PK		×
14.2.6b	[redacted]	PD	×	×
14.2.6d		PD		×
14.2.7d		PD		×
14.2.8d		PD		×
14.2.9d		PD		×
14.2.10d		PD		×
14.2.11d		PD		×
14.2.12b		PD	×	×
14.2.13b		PD	×	×
14.2.14b		PD	×	×
14.2.15b		PD	×	×
14.2.16d		PD		
14.2.16e		PD		
14.3	**Safety**			
14.3.1a	Concomitant Medications by ATC Classification – SAD-HS	Safety	×	×
14.3.1b	Concomitant Medications by ATC Classification – MAD-HS	Safety	×	×
14.3.1c	Concomitant Medications by ATC Classification – SD-CP/SD-UP	Safety		×
14.3.1d	Concomitant Medications by ATC Classification – MAD-CP/MAD-UP	Safety		×

Table Number	Table Title	Population	Interim	Final
14.3.1e	Concomitant Medications by ATC Classification – FE-HS	Safety		
14.3.3	**Adverse Events**			
14.3.3.1a	Summary of Treatment Emergent Adverse Events – SAD-HS	Safety	×	×
14.3.3.1b	Summary of Treatment Emergent Adverse Events – MAD-HS	Safety	×	×
14.3.3.1c	Summary of Treatment Emergent Adverse Events – SD-CP/SD-UP	Safety		×
14.3.3.1d	Summary of Treatment Emergent Adverse Events – MAD-CP/MAD-UP	Safety		×
14.3.3.1e	Summary of Treatment Emergent Adverse Events – FE-HS	Safety		
14.3.3.2a	Incidence of Treatment-Emergent Adverse Events by SOC and PT – SAD-HS	Safety	×	×
14.3.3.2b	Incidence of Treatment-Emergent Adverse Events by SOC and PT – MAD-HS	Safety	×	×
14.3.3.2c	Incidence of Treatment-Emergent Adverse Events by SOC and PT – SD-CP/SD-UP	Safety		×
14.3.3.2d	Incidence of Treatment-Emergent Adverse Events by SOC and PT – MAD-CP/MAD-UP	Safety		×
14.3.3.2e	Incidence of Treatment-Emergent Adverse Events by SOC and PT – FE-HS	Safety		
14.3.3.3a	Incidence of Treatment-Emergent Adverse Events by SOC, PT and Maximum Severity – SAD-HS	Safety	×	×
14.3.3.3b	Incidence of Treatment-Emergent Adverse Events by SOC, PT and Maximum Severity – MAD-HS	Safety	×	×
14.3.3.3c	Incidence of Treatment-Emergent Adverse Events by SOC, PT and Maximum Severity – SD-CP/SD-UP	Safety		×
14.3.3.3d	Incidence of Treatment-Emergent Adverse Events by SOC, PT and Maximum Severity – MAD-CP/MAD-UP	Safety		×
14.3.3.3e	Incidence of Treatment-Emergent Adverse Events by SOC, PT and Maximum Severity – FE-HS	Safety		
14.3.3.4a	Incidence of Serious Treatment-Emergent Adverse Events by SOC and PT – SAD-HS	Safety	×	×

Table Number	Table Title	Population	Interim	Final
14.3.3.4b	Incidence of Serious Treatment-Emergent Adverse Events by SOC and PT – MAD-HS	Safety	×	×
14.3.3.4c	Incidence of Serious Treatment-Emergent Adverse Events by SOC and PT – SD-CP/SD-UP	Safety		×
14.3.3.4d	Incidence of Serious Treatment-Emergent Adverse Events by SOC and PT – MAD-CP/MAD-UP	Safety		×
14.3.3.4e	Incidence of Serious Treatment-Emergent Adverse Events by SOC and PT – FE-HS	Safety		
14.3.3.5a	Incidence of Drug-Related Treatment-Emergent Adverse Events by SOC and PT – SAD-HS	Safety	×	×
14.3.3.5b	Incidence of Drug-Related Treatment-Emergent Adverse Events by SOC and PT – MAD-HS	Safety	×	×
14.3.3.5c	Incidence of Drug-Related Treatment-Emergent Adverse Events by SOC and PT – SD-CP/SD-UP	Safety		×
14.3.3.5d	Incidence of Drug-Related Treatment-Emergent Adverse Events by SOC and PT – MAD-CP/MAD-UP	Safety		×
14.3.3.5e	Incidence of Drug-Related Treatment-Emergent Adverse Events by SOC and PT – FE-HS	Safety		
14.3.3.6a	Incidence of Treatment-Emergent Adverse Events Leading to Study Treatment Withdrawal by SOC and PT – SAD-HS	Safety	×	×
14.3.3.6b	Incidence of Treatment-Emergent Adverse Events Leading to Study Treatment Withdrawal by SOC and PT – MAD-HS	Safety	×	×
14.3.3.6c	Incidence of Treatment-Emergent Adverse Events Leading to Study Treatment Withdrawal by SOC and PT – SD-CP/SD-UP	Safety		×
14.3.3.6d	Incidence of Treatment-Emergent Adverse Events Leading to Study Treatment Withdrawal by SOC and PT – MAD-CP/MAD-UP	Safety		×
14.3.3.6e	Incidence of Treatment-Emergent Adverse Events Leading to Study Treatment Withdrawal by SOC and PT – FE-HS	Safety		
14.3.4	**Laboratory Parameters**			×
14.3.4.1.1a	Hematology Results - Change of Hematology Values – SAD-HS	Safety	×	×

Table Number	Table Title	Population	Interim	Final
14.3.4.1.1b	Hematology Results - Change of Hematology Values – MAD-HS	Safety	×	×
14.3.4.1.1c	Hematology Results - Change of Hematology Values – SD-CP/SD-UP	Safety		×
14.3.4.1.1d	Hematology Results - Change of Hematology Values – MAD-CP/MAD-UP	Safety		×
14.3.4.1.1e	Hematology Results - Change of Hematology Values – FE-HS	Safety		
14.3.4.1.2a	Hematology Results - Out of Normal Range Values – SAD-HS	Safety	×	×
14.3.4.1.2b	Hematology Results - Out of Normal Range Values – MAD-HS	Safety	×	×
14.3.4.1.2c	Hematology Results - Out of Normal Range Values – SD-CP/SD-UP	Safety		×
14.3.4.1.2d	Hematology Results - Out of Normal Range Values – MAD-CP/MAD-UP	Safety		×
14.3.4.1.2e	Hematology Results - Out of Normal Range Values – FE-HS	Safety		
14.3.4.1.3a	Hematology Results - Normal/Abnormal Shift Table – SAD-HS	Safety	×	×
14.3.4.1.3b	Hematology Results - Normal/Abnormal Shift Table – MAD-HS	Safety	×	×
14.3.4.1.3c	Hematology Results - Normal/Abnormal Shift Table – SD-CP/SD-UP	Safety		×
14.3.4.1.3d	Hematology Results - Normal/Abnormal Shift Table – MAD-CP/MAD-UP	Safety		×
14.3.4.1.3e	Hematology Results - Normal/Abnormal Shift Table – FE-HS	Safety		
14.3.4.2.1a	Chemistry Results - Change of Chemistry Values – SAD-HS	Safety	×	×
14.3.4.2.1b	Chemistry Results - Change of Chemistry Values – MAD-HS	Safety	×	×
14.3.4.2.1c	Chemistry Results - Change of Chemistry Values – SD-CP/SD-UP	Safety		×
14.3.4.2.1d	Chemistry Results - Change of Chemistry Values – MAD-CP/MAD-UP	Safety		×
14.3.4.2.1e	Chemistry Results - Change of Chemistry Values – FE-HS	Safety		
14.3.4.2.2a	Chemistry Results - Out of Normal Range Values – SAD-HS	Safety	×	×
14.3.4.2.2b	Chemistry Results - Out of Normal Range Values – MAD-HS	Safety	×	×

Table Number	Table Title	Population	Interim	Final
14.3.4.2.2c	Chemistry Results - Out of Normal Range Values – SD-CP/SD-UP	Safety		×
14.3.4.2.2d	Chemistry Results - Out of Normal Range Values – MAD-CP/MAD-UP	Safety		×
14.3.4.2.2e	Chemistry Results - Out of Normal Range Values – FE-HS	Safety		
14.3.4.2.3a	Chemistry Results - Normal/Abnormal Shift Table – SAD-HS	Safety	×	×
14.3.4.2.3b	Chemistry Results - Normal/Abnormal Shift Table – MAD-HS	Safety	×	×
14.3.4.2.3c	Chemistry Results - Normal/Abnormal Shift Table – SD-CP/SD-UP	Safety		×
14.3.4.2.3d	Chemistry Results - Normal/Abnormal Shift Table – MAD-CP/MAD-UP	Safety		×
14.3.4.2.3e	Chemistry Results - Normal/Abnormal Shift Table – FE-HS	Safety		
14.3.4.3.1a	Urinalysis Results - Change of Urinalysis Values – SAD-HS	Safety	×	×
14.3.4.3.1b	Urinalysis Results - Change of Urinalysis Values – MAD-HS	Safety	×	×
14.3.4.3.1c	Urinalysis Results - Change of Urinalysis Values – SD-CP/SD-UP	Safety		×
14.3.4.3.1d	Urinalysis Results - Change of Urinalysis Values – MAD-CP/MAD-UP	Safety		×
14.3.4.3.1e	Urinalysis Results - Change of Urinalysis Values – FE-HS	Safety		
14.3.4.3.2a	Urinalysis Results - Out of Normal Range Values – SAD-HS	Safety	×	×
14.3.4.3.2b	Urinalysis Results - Out of Normal Range Values – MAD-HS	Safety	×	×
14.3.4.3.2c	Urinalysis Results - Out of Normal Range Values – SD-CP/SD-UP	Safety		×
14.3.4.3.2d	Urinalysis Results - Out of Normal Range Values – MAD-CP/MAD-UP	Safety		×
14.3.4.3.2e	Urinalysis Results - Out of Normal Range Values – FE-HS	Safety		
14.3.4.3.3a	Urinalysis Results - Normal/Abnormal Shift Table – SAD-HS	Safety	×	×
14.3.4.3.3b	Urinalysis Results - Normal/Abnormal Shift Table – MAD-HS	Safety	×	×
14.3.4.3.3c	Urinalysis Results - Normal/Abnormal Shift Table – SD-CP/SD-UP	Safety		×
14.3.4.3.3d	Urinalysis Results - Normal/Abnormal Shift Table – MAD-CP/MAD-UP	Safety		×

Table Number	Table Title	Population	Interim	Final
14.3.4.3.3e	Urinalysis Results - Normal/Abnormal Shift Table – FE-HS	Safety		
14.3.5	**Other Safety**			
14.3.5.1a	Vital Signs - Values and Change from Baseline – SAD-HS	Safety	×	×
14.3.5.1b	Vital Signs - Values and Change from Baseline – MAD-HS	Safety	×	×
14.3.5.1c	Vital Signs - Values and Change from Baseline – SD-CP/SD-UP	Safety		×
14.3.5.1d	Vital Signs - Values and Change from Baseline – MAD-CP/MAD-UP	Safety		×
14.3.5.1e	Vital Signs - Values and Change from Baseline – FE-HS	Safety		
14.3.5.2a	12-Lead ECG Results - Change of 12-Lead ECG Values – SAD-HS	Safety	×	×
14.3.5.2b	12-Lead ECG Results - Change of 12-Lead ECG Values – MAD-HS	Safety	×	×
14.3.5.2c	12-Lead ECG Results - Change of 12-Lead ECG Values – SD-CP/SD-UP	Safety		×
14.3.5.2d	12-Lead ECG Results - Change of 12-Lead ECG Values – MAD-CP/MAD-UP	Safety		×
14.3.5.2e	12-Lead ECG Results - Change of 12-Lead ECG Values – FE-HS	Safety		
14.3.5.3a	12-Lead ECG Results - Normal/Abnormal Shift Table – SAD-HS	Safety	×	×
14.3.5.3b	12-Lead ECG Results - Normal/Abnormal Shift Table – MAD-HS	Safety	×	×
14.3.5.3c	12-Lead ECG Results - Normal/Abnormal Shift Table – SD-CP/SD-UP	Safety		×
14.3.5.3d	12-Lead ECG Results - Normal/Abnormal Shift Table – MAD-CP/MAD-UP	Safety		×
14.3.5.3e	12-Lead ECG Results - Normal/Abnormal Shift Table – FE-HS	Safety		
14.3.5.4c	Hemodialysis – SD-UP	Safety		×
14.3.5.4d	Hemodialysis – MAD-UP	Safety		×

19. LISTINGS

Listing Number	Listing Title	Population	Interim	Final
16.2.1	**Subject Disposition**			
16.2.1.1	Analysis Populations	Enrolled	x	x
16.2.1.1e	Analysis Populations – FE-HS	Enrolled		
16.2.1.2	Subject Disposition	Enrolled	x	x
16.2.1.2e	Subject Disposition – FE-HS	Enrolled		
16.2.1.3	Subject Visits	Enrolled	x	x
16.2.1.3e	Subject Visits – FE-HS	Enrolled		
16.2.1.4	Subject Admission	Enrolled	x	x
16.2.1.4e	Subject Admission – FE-HS	Enrolled		
16.2.1.5	Screen Failures	Screen Failures	x	x
16.2.2	**Protocol Deviations**			
16.2.2.1	Protocol Deviations	Enrolled	x	x
16.2.2.1e	Protocol Deviations – FE-HS	Enrolled		
16.2.4	**Demographic and Other Baseline Data**			
16.2.4.1	Demographics and Baseline Characteristics	Enrolled	x	x
16.2.4.1e	Demographics and Baseline Characteristics – FE-HS	Enrolled		
16.2.4.2	Medical History	Enrolled	x	x
16.2.4.2e	Medical History – FE-HS	Enrolled		
16.2.4.3	Disease History	Enrolled		x
16.2.4.4	Itch History	Enrolled		x
16.2.4.5	Hemodialysis History	Enrolled		x
16.2.4.6	Drug Screening and Other Screening Labs	Enrolled	x	x
16.2.4.6e	Drug Screening and Other Screening Labs – FE-HS	Enrolled		

Listing Number	Listing Title	Population	Interim	Final
16.2.4.7	Inclusion/ Exclusion Criteria	Enrolled	x	x
16.2.4.7e	Inclusion/ Exclusion Criteria – FE-HS	Enrolled		
16.2.5	**Treatment Administration**			
16.2.5.1	Subject Randomization	Enrolled	x	x
16.2.5.1e	Subject Randomization – FE-HS	Enrolled		
16.2.5.2	Study Drug Administration	Enrolled	x	x
16.2.5.2e	Study Drug Administration – FE-HS	Enrolled		
16.2.6	**Efficacy/PK/PD**			
16.2.6.1	Plasma EP547 & EP3583 Concentrations	Enrolled	x	x
16.2.6.1e	Plasma EP547 Concentrations – FE-HS	Enrolled		
16.2.6.2	Plasma EP547 & EP3583 PK Parameters	PK	x	x
16.2.6.2e	Plasma EP547 PK Parameters – FE-HS	PK		
16.2.6.3	Urine EP547 and EP3583 PK Concentration	Enrolled	x	x
16.2.6.4	Urine EP547 and EP3583 PK Parameters	Urine PK	x	x
16.2.6.5	PK Skin Biopsy	Enrolled	x	x
16.2.6.6	[redacted]	Enrolled	x	x
16.2.6.7	[redacted]	Enrolled		x
16.2.6.8	[redacted]	Enrolled		x
16.2.6.9	[redacted]	Enrolled		x
16.2.6.10	[redacted]	Enrolled		x
16.2.6.11	[redacted]	Enrolled		x
16.2.6.12	[redacted]	Enrolled		x
16.2.6.13	[redacted]	Enrolled		x
16.2.6.14	[redacted]	Enrolled		x

Listing Number	Listing Title	Population	Interim	Final
16.2.6.15	[redacted]	Enrolled		x
16.2.6.16	[redacted]	Enrolled	x	x
16.2.6.17	[redacted]	Enrolled		
16.2.6.17e	[redacted]	Enrolled		
16.2.7	**Adverse Events**			
16.2.7.1	Adverse Events	Enrolled	x	x
16.2.7.1e	Adverse Events – FE-HS	Enrolled		
16.2.7.2	Serious Adverse Events	Enrolled	x	x
16.2.7.2e	Serious Adverse Events – FE-HS	Enrolled		
16.2.7.3	Drug-Related Adverse Events	Enrolled	x	x
16.2.7.3e	Drug-Related Adverse Events – FE-HS	Enrolled		
16.2.7.4	Adverse Events Leading to Study Drug Discontinuation	Enrolled	x	x
16.2.7.4e	Adverse Events Leading to Study Drug Discontinuation – FE-HS	Enrolled		
16.2.7.5	Adverse Events with Outcome of Death	Enrolled	x	x
16.2.7.5e	Adverse Events with Outcome of Death – FE-HS	Enrolled		
16.2.8	**Laboratory Parameters**			
16.2.8.1	Hematology Results	Enrolled	x	x
16.2.8.1e	Hematology Results – FE-HS	Enrolled		
16.2.8.2	Chemistry Results	Enrolled	x	x
16.2.8.2e	Chemistry Results – FE-HS	Enrolled		
16.2.8.3	Urinalysis Results	Enrolled	x	x
16.2.8.3e	Urinalysis Results – FE-HS	Enrolled		

Listing Number	Listing Title	Population	Interim	Final
16.2.9	**Other Safety**			
16.2.9.1	Vital Signs	Enrolled	x	x
16.2.9.1e	Vital Signs – FE-HS	Enrolled		
16.2.9.2	12-Lead Electrocardiogram	Enrolled	x	x
16.2.9.2e	12-Lead Electrocardiogram – FE-HS	Enrolled		
16.2.9.3	Physical Examination	Enrolled	x	x
16.2.9.3e	Physical Examination – FE-HS	Enrolled		
16.2.9.4	Hemodialysis	Enrolled	x	x
16.2.9.5	Holter Monitoring	Enrolled	x	x
16.2.10	**Prior & Concomitant Medication**			
16.2.10	Prior and Concomitant Medication	Enrolled	x	x
16.2.10e	Prior and Concomitant Medication – FE-HS	Enrolled		
16.2.11	**Comments**			
16.2.11	Comment Log	Enrolled	x	x

20. FIGURES

Novotech is not responsible to generate Figures for this study.

21. REFERENCES

Protocol Original dated 17 June 2020

Protocol Amendment 1.0 dated 14 December 2020

Protocol Amendment 2.0 dated 19 February 2021

Clinical Study Protocol Addendum 1.0 to Amendment 2.0 Version dated 19 March 2021

Annotated CRF version dated 15 April 2021

[redacted]