# Statistical Analysis Plan

A Phase Ia Clinical Study of HIV Entry Inhibitor CPT31: Single Ascending Dose Study of Safety, Tolerability, Immunogenicity, and Pharmacokinetics in Healthy Adults

**NCT Number**

NCT04672083

**Document Date**

August 13, 2020

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## A Phase Ia Clinical Study of HIV Entry Inhibitor CPT31: Single Ascending Dose Study of Safety, Tolerability, Immunogenicity, and Pharmacokinetics in Healthy Adults

SAP Status: Final
SAP Version: 1.0
SAP Date: 13 August 2020

Investigational Product: CPT31

Protocol Reference: CPT31-001
Covance Study: 8405732

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## LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

| | |
|---|---|
| ADaM | analysis data model |
| $\%AUC_{extrap}$ | percentage of AUC due to extrapolation from the last quantifiable concentration to infinity |
| AE | adverse event |
| $A_e$ | amount of drug excreted in the urine at each collection interval and cumulative amount of drug excreted in the urine at each collection interval |
| ANOVA | analysis of variance |
| AUC0-∞ | area under the curve from time 0 to infinity |
| $AUC_{0\text{-}tlast}$ | area under the curve from time 0 to the time of the last measurable concentration |
| BLQ | below the limit of quantification |
| CDISC | Clinical Data Interchange Standards Consortium |
| CI | confidence interval |
| CL/F | apparent total plasma clearance |
| $CL_R$ | renal clearance |
| $C_{max}$ | maximum concentration |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | coefficient of variation |
| ECG | Electrocardiogram |
| $F_e$ | percentage excreted in urine at each collection interval and cumulative percentage excreted in urine at each collection interval |
| GLSM | geometric least squares mean |
| ICH | International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| LLOQ | lower limit of quantification |
| Ln | natural log |
| LSM | least squares mean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PK | pharmacokinetic(s) |
| QTc | QT interval corrected for heart rate |
| QTcB | QT interval corrected for heart rate using Bazett's formula |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| SAP | statistical analysis plan |

| | |
|---|---|
| SD | standard deviation |
| $t_{1/2}$ | apparent terminal elimination half-life |
| TEAE | treatment-emergent adverse event |
| TFL | table, figure, and listing |
| $T_{last}$ | time of the last quantifiable plasma concentration |
| $T_{max}$ | time to maximum concentration |
| $V_z/F$ | Apparent volume of distribution during the terminal elimination phase |
| WHODrug | World Health Organization Drug Dictionary |

# 1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 4.0 dated 27 July 2020) and electronic case report form.

This SAP describes the planned analysis of the pharmacokinetic (PK) and safety and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Navigen Inc. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are approved, they will serve as the template for this study's CSR.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Navigen Inc. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline *Statistical Principles for Clinical Trials* and ICH E3 guideline *Structure and Content of Clinical Study Reports*.[1,2]

The document history is presented in Appendix 1.

# 2. STUDY OBJECTIVES

The primary objective of the study is:

• to assess the safety and tolerability of a single SC dose of CPT31 in healthy subjects

The secondary objectives of the study are:

• to characterize the single SC dose PK of CPT31

• to identify and characterize antibodies to CPT31

# 3. STUDY ENDPOINTS

## 3.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

• incidence and severity of adverse events (AEs)

• incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results

• 12-lead electrocardiogram (ECG) parameters

• vital signs measurements

• physical examinations

• anti-CPT31 antibodies, e.g., immunoglobulin (Ig)G, IgM

### 3.2. Secondary Endpoints

The single ascending dose PK outcome endpoints of CPT31 are as follows:

• AUC from time zero to infinity ($AUC_{0-\infty}$)

• AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$)

• $C_{max}$

• time of the maximum observed plasma concentration ($T_{max}$)

• $t_{1/2}$

• apparent total plasma clearance (CL/F)

• apparent volume of distribution ($V_z$/F)

• renal clearance ($CL_R$)

• amount of drug excreted in the urine ($A_e$)

• percentage of dose excreted unchanged in the urine ($F_e$)

Other PK parameters may also be reported.

## 4. STUDY DESIGN

This study will comprise a placebo-controlled, double-blind, single-dose, sequential-group design. Overall, it is planned for 32 healthy subjects to be studied in 4 groups (Groups A1 to A4), with each group consisting of 8 subjects. In each group, 6 subjects will be randomized to receive SC CPT31 and 2 subjects will be randomized to receive matching placebo.

All groups will be divided into 2 cohorts, with each cohort being dosed 72 hours apart. The first (sentinel) cohort will comprise 2 subjects, with 1 subject receiving CPT31 and 1 subject receiving placebo. The second cohort will comprise 6 subjects, with 5 subjects receiving CPT31 and 1 subject receiving placebo.Potential subjects will be screened to assess their eligibility to enter the study within 28 days
prior to the first dose administration.

Each subject will participate in 1 treatment period only. Subjects will reside at the Clinical Research Unit (CRU) from Day -1 (the day before dosing) to Day 6. All subjects will return

for a Follow-up visit 28 to 30 days after dosing.

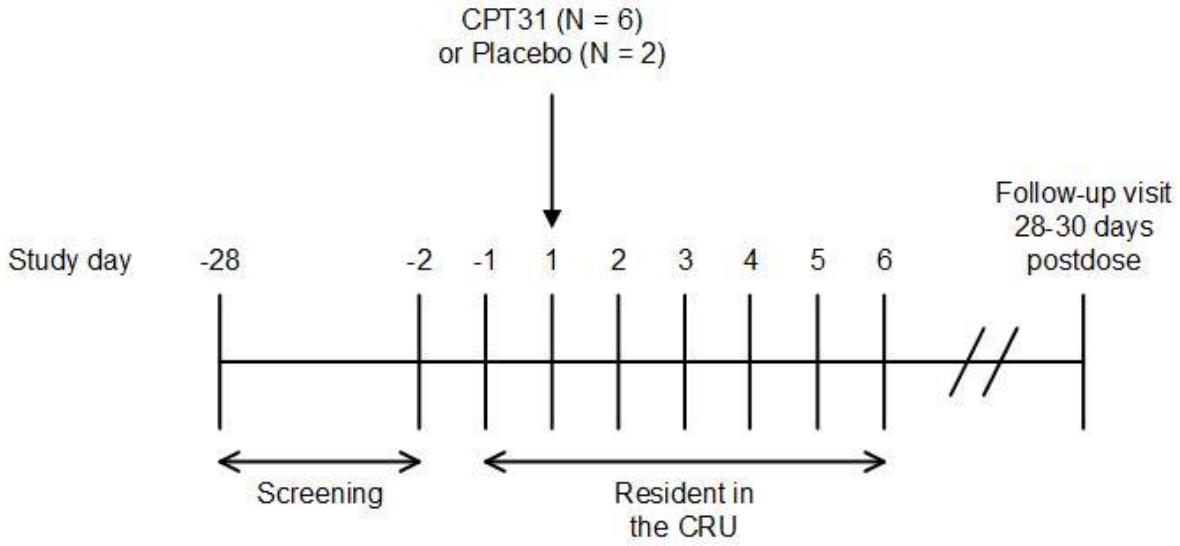
Based on the ongoing review of the safety, tolerability, and PK results, additional nonresidential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond 30 days after dose administration.

The maximum total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

Dose escalation will occur a minimum of 7 days after all subjects complete all Day 6 assessments in the previous dose group.

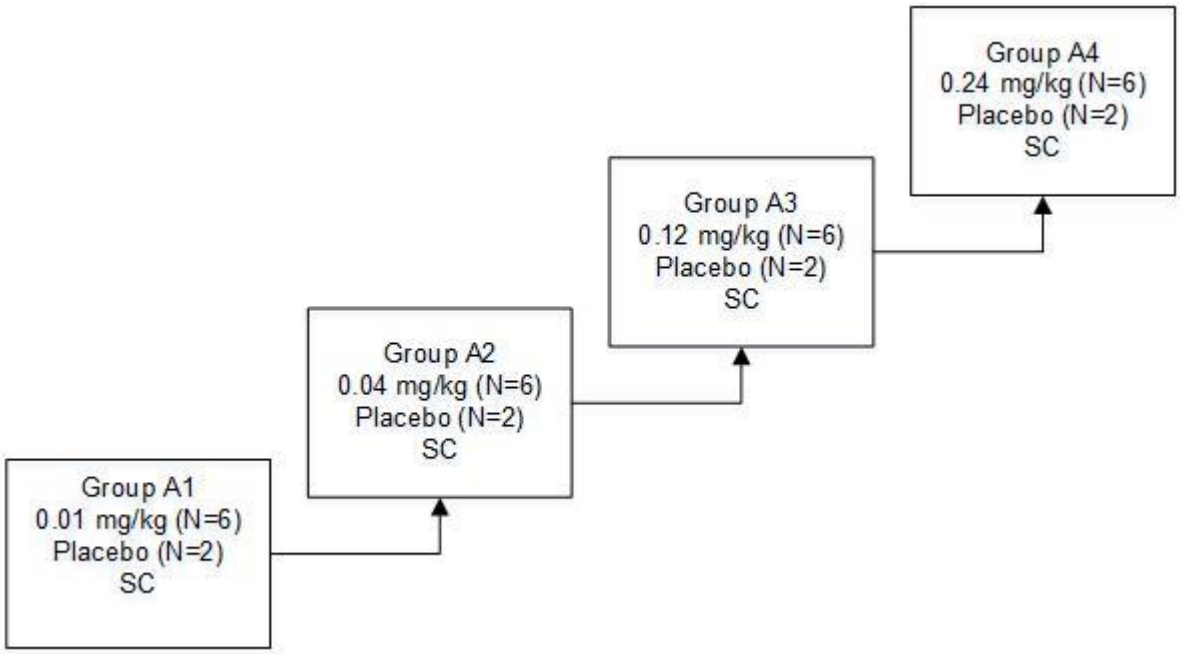
An overview of the study design is shown in Figure 1 and the planned dose levels are shown in Figure 2.

**Figure 1: Study Schematic**




Abbreviations: CRU = Clinical Research Unit, N = number of subjects.

**Figure 2: Planned Dose Levels**




Abbreviations: N = number of subjects; SC = subcutaneous.

## 5. SAMPLE SIZE JUSTIFICATION

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time CPT31 is being administered to humans. However, the number of subjects in the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. A common distribution between active and placebo subjects is 6+2. Buoen et al. (Evaluation of the Cohort Size in Phase I Dose Escalation Trials Based on Laboratory Data, J Clin Pharmacol (2003) 43:470-476) investigated the impact of cohort size on Type I error and power in Phase I dose escalation trials based on laboratory data and concluded that "the active cohort size in Phase I dose escalation trials should be between 6 and 10 active subjects."

## 6. STUDY TREATMENTS

The study treatment names, abbreviations, and ordering to be used in the TFLs are presented in Table 1.

**Table 1: Presentation of Study Treatment Sequences in TFLs**

| Study Treatment Name | Treatment Order on TFLs |
|---|---|
| Placebo | 1 |
| 0.01 mg/kg SC CPT31 | 2 |

| | |
|---|---|
| 0.04 mg/kg SC CPT31 | 3 |
| 0.12 mg/kg SC CPT31 | 4 |
| 0.24 mg/kg SC CPT31 | 5 |

## 7. DEFINITIONS OF POPULATIONS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

### 7.1. All Subjects Population

The all-subjects population will include all subjects who signed the informed consent form and had any study assessment recorded in the database per the protocol.

### 7.2. Safety Population

The safety population will include all subjects who received at least 1 dose of study treatment (CPT31 or placebo).

### 7.3. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of CPT31 and have evaluable PK data.

## 8. STATISTICAL METHODOLOGY

### 8.1. General

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to the all-subjects population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they completed all protocol-specified procedures and assessments for the end-of-treatment visit. Any subject who discontinued the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if upversioned during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if upversioned during the study) and CDISC ADaM Implementation Guide Version 1.2 (or higher if upversioned during the study). Pinnacle 21 Community Validator Version 2.2.0 (or higher if upversioned during the study) will be utilized to ensure compliance with CDISC standards.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline, percentage changes from baseline, and any parameter derivations.

### 8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- As Early Termination data is not associated with any scheduled timepoint, it will be excluded from all calculations of summary statistics.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.
- Missing values will not be imputed, with the exception of AEs where the 'worst-case' approach will be taken (see Section 8.6.1), or unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

### 8.1.2. Triplicate Readings

For vital signs data only, where triplicate readings are taken, the median of triplicate readings will replace the original readings in all calculations.

For electrocardiogram (ECG) data only, where triplicate readings are taken, the mean of triplicate readings will replace the original readings in all calculations.

In case of incomplete triplicate readings (eg, only 2 out of 3 readings were recorded), the mean and/or medians will be calculated based on the number of readings available.

### 8.1.3. Repeat and Unscheduled Readings

For vital signs and ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will

be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 8.1.4).

### 8.1.4. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last value recorded prior to dosing. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The mean change from baseline will be defined as the mean of the individual changes from baseline for all subjects.

See Section 8.1.3 for more detail on handling repeat and unscheduled readings in the calculations. See Section 8.1.2 for more detail on handling of triplicate readings in the calculations.

## 8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by treatment will be provided, based on the all-subjects population.

## 8.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table by treatment will be provided, based on the safety population.

## 8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to dosing. Concomitant medication will be defined as medication that starts during or after dosing or starts but does not end prior to dosing.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version March 2020 (or later if upversioned during the study). Prior and concomitant medications will be listed.

## 8.5. Pharmacokinetic Assessments

### 8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of CPT31, using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara USA, Inc., Version 8.1 or higher):

| Parameter | Units | Definition |
|---|---|---|
| $AUC_{0\text{-}tlast}$ | h*xg/mL | area under the curve from time 0 to the time of the last measurable concentration[a] |
| $AUC_{0\text{-}\infty}$ | h*xg/mL | area under the curve from time 0 to infinity[b] |
| $C_{max}$ | xg/mL | maximum concentration |
| $T_{max}$ | h | time to maximum concentration |
| $T_{last}$ | h | time of the last quantifiable plasma concentration |
| $t_{1/2}$ | h | apparent terminal elimination half-life |
| CL/F | L/h | apparent total plasma clearance |
| $V_z$/F | L | Apparent volume of distribution during the terminal elimination phase |
| $\%AUC_{extrap}$ | % | percentage of AUC due to extrapolation from the last quantifiable concentration to infinity |
| $A_e$ | mg | amount of drug excreted in the urine at each collection interval and cumulative amount of drug excreted in the urine at each collection interval |
| $F_e$ | % | percentage excreted in urine at each collection interval and cumulative percentage excreted in urine at each collection interval |
| CLR | h*xg/mL/mg | renal clearance |

a AUC will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule). Additional pharmacokinetic parameters may be determined where appropriate.
b Based on last observed quantifiable concentration

Additional PK parameters may be determined where appropriate.

Actual elapsed time from dosing will be used to estimate all individual PK parameters. If actual times are missing, nominal times may be used by default.

If $AUC_{0\text{-}\infty}$ cannot be determined for all subjects, an alternative AUC measure, such as AUC to a fixed time point, may be used in the statistical analysis.

$C_{max}$, $T_{max}$ and $T_{last}$ will be obtained directly from the concentration-time profiles. For multiple peaks, the highest postdose concentration will be reported as $C_{max}$. In the case that multiple peaks are of equal magnitude, the earliest $T_{max}$ will be reported.

The amount of drug excreted in urine ($A_e$) and percentage of dose excreted ($F_e$) will be calculated for each urine collection ($t_1$-$t_2$); cumulative $A_e$ and $F_e$ will be calculated by

summing the $t_1$-$t_2$ values over the 0-t2 period where t2 = end of the study collection period. $A_e$ will be calculated using a urine density of 1.0 g/mL.

$CL_R$ will be calculated over the same collection interval according to the following formula, at the time interval (0-t2) where concentrations are quantifiable for both parameters:

$$CL_R = \frac{Ae_{0\text{-}t2}}{AUC_{0-t2}}$$

#### 8.5.1.1. Criteria for Handling Concentrations Below the Limit of Quantification or Missing Concentrations in Pharmacokinetic Analysis

For the non-compartmental analysis (NCA) and individual plot, if a BLQ value occurs before the first measurable concentration, it will be assigned a value of 0, otherwise it will be treated as missing. The following rules apply with special situations defined below:

- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless they are considered to be a true characteristic of the profile of the drug.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a pre-dose measurement for the first dose is missing, the value will be set to zero.

#### 8.5.1.2. Criteria for Calculating an Apparent Terminal Elimination Half-life

The start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations.

The apparent terminal elimination rate constant ($\lambda_z$) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including $C_{max}$, and the adjusted coefficient for determination of exponential fit ($R^2$-adj) of the regression line is ≥0.7. Parameters requiring $\lambda_z$ in their calculation (eg, $AUC_{0\text{-inf}}$, $t_{1/2}$, CL/F and $V_z$/F) will only be calculated if the $R^2$-adj value of the regression line is ≥0.7.

The following regression-related diagnostic PK parameters will be determined:

| Parameter | Units | Definition |
|---|---|---|
| $\lambda_z$ | $h^{-1}$ | apparent terminal elimination rate constant |
| $\lambda_z$ Upper | h | end of exponential fit |
| $\lambda_z$ Lower | h | start of exponential fit |
| $\lambda_z$ N | NA | number of data points included in the log-linear regression |
| $\lambda_z$ Span Ratio | NA | time period over which $\lambda_z$ was determined as a ratio of $t_{1/2}$ |
| $R^2$-adj | NA | adjusted coefficient for determination of exponential fit |

The time period used for the estimation of apparent terminal elimination half-lives, where possible, will be over at least two half-lives. For $t_{1/2}$ estimates where $\lambda_z$ was calculated over a time period less than twice their resultant half-life, the reliability of $t_{1/2}$ and any PK parameters derived from $\lambda_z$ will be discussed in CSR.

#### 8.5.1.3. Criteria for Calculating AUC

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow $C_{max}$.

If the extrapolated area is 30%, $AUC_{0-\infty}$ (and derived parameters CL/F, $V_z$/F, $t_{1/2}$ etc) may be excluded from summary statistics and statistical analysis at the discretion of the sponsor or PK analyst.

#### 8.5.1.4. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in CSR.

Quantifiable predose concentration values in the first dosing will be considered anomalous and set to missing for the PK analysis.

### 8.5.2. Presentation of Pharmacokinetic Data

#### 8.5.2.1. Presentation of Plasma Drug Concentration Data

If the actual time of sample collection deviates from the nominal time by more than ±10%, the concentration will be flagged and excluded from the summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For PK concentration data the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and coefficient of variation (CV%) of geometric mean will be reported as not calculated (NC).

#### 8.5.2.2. Presentation of Plasma Pharmacokinetic Parameter Data

The PK parameters will be listed and summarized descriptively by treatment (arithmetic and geometric means; standard deviation and CV%; minimum, maximum, and median values; and geometric CV). For $T_{max}$ and $T_{last}$, no geometric mean and geometric CV will be calculated.

For the calculation of summary statistics of PK parameters, all not reported (NR) and NC values in a data series will be set to missing.

### 8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables, mean (± standard deviation [SD]) figures, overlaying individual figures, and individual figures by treatment and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear and semi-logarithmic scales, with the exception of figures across all days, which will be produced on the linear scale only. The +SD bars will only be displayed on the linear scale.

Summary tables by treatment will be provided for all PK parameters, with the exception of diagnostic regression-related PK parameters. Separate summary tables by treatment and time interval will be provided for excretion parameters and cumulative excretion parameters.

Where data are available, CPT31 dose proportionality will be examined across dose groups. The PK parameters ($C_{max}$, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$) will be analysed for dose proportionality using a power model approach or analysis of variance (ANOVA) model, as appropriate. The PK parameters will be analyzed using a power model[3] that will have the following form:

$$parameter = intercept \times dose\text{^}slope + random\ error$$

Using the natural log (ln) transformation,[4] a power model can be expressed as a linear regression equation:

$$ln(parameter) = intercept + slope \times ln(dose) + random\ error$$

For dose proportionality, the slope of the regression line is equal to 1; for dose independence, it is equal to 0.

For each PK parameter separately, a pooled estimate (across all doses) of slope, corresponding 95% confidence interval (CI), and between-subject CV will be calculated. Figures (on the logarithmic scale) containing individual values, power model line (95% CI), and dose proportionality line (defined as the power model line with slope of 1) will be created for each PK parameter; figures (on the semi-logarithmic scale) containing individual values and geometric means will be created for each corresponding PK parameter normalized by dose administered.

The lack of fit test will be conducted for the statistical assessment of linearity assumption, and thus appropriateness of a power model. The lack of fit model will be the same as the power model fitted, but with dose included as additional fixed effect. The statistical assessment will rule the linearity assumption acceptable if the diagnostic plots appear reasonable and the lack of fit p-value >0.05 (dose effect is not significant at the 0.05 level of significance). The assessment of linearity assumption may also occur via visual examination of the figures by the pharmacokineticist. This assessment may override the statistical assessment; where this occurs, it will be detailed in the CSR.

It will be concluded that PK parameter is dose proportional for the dose range studied if the assumption of linearity is ruled acceptable and the 95% CI for the slope spans 1.

If the assumption of linearity is ruled unacceptable for any PK parameter, its corresponding PK parameter normalized by dose administered will be ln-transformed and analyzed using an analysis of variance (ANOVA) model.[6] The model will include dose as a factor.

For each PK parameter separately, the geometric least squares mean (GLSM) for each dose, p-values for the overall, and pairwise dose comparisons will be calculated. Residual plots will be produced to assess the adequacy of the model(s) fitted.

Examples of the SAS code that will be used are as follows:

**Power Model Analysis**

```
proc mixed data = <data in> alpha = 0.05;
 by parcat1n parcat1 pkday paramn param;
 class usubjid;
 model lpk = ldose / cl residual ddfm = kr;
 random intercept / subject = usubjid;
 ods output solutionf = <data out>;
run;
```

**Power Model Analysis (Lack of Fit Test)**

```
proc mixed data = <data in>;
 by parcat1n parcat1 pkday paramn param;
 class dose usubjid;
 model lpk = ldose dose / htype = 1 ddfm = kr;
 random intercept / subject = usubjid;
 ods output tests1 = <data out>;
run;
```

**ANOVA Model Analysis**

```
proc mixed data = <data in> alpha = 0.05;
 by parcat1n parcat1 pkday paramn param;
 class dose;
 model ldnpk = dose / cl residual ddfm = kr;
 lsmeans dose / cl pdiff;
 ods output lsmeans = <data out>;
 ods output diffs = <data out>;
 ods output tests3 = <data out>;
run;
```

No inferential statistical analyses are planned.

## 8.6. Safety and Tolerability Assessments

### 8.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 (or higher if upversioned during the study). All AEs will be assigned severity grade using the following criteria defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017:

- **Grade 1, Mild:** Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- **Grade 2, Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Grade 3, Severe**: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- **Grade 4, Potentially Life-threatening:** The subject was at immediate risk of death from the event as it occurred (i.e., does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
- **Grade 5, Death.**

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after dosing, or starts prior to dosing and increases in severity after dosing.

A treatment-related TEAE will be defined as a TEAE with a relationship of possibly, probably, or definitely related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing for TEAEs only.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to dosing.

- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.

- For the derivation of onset time: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of dosing is 01MAY2019/08:00 and recorded start date/time of an AE is 03MAY2019, then the minimum possible onset time will be calculated by assuming the AE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).

- For the derivation of duration: If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).

- For the calculation of summary statistics: If the severity of a TEAE is missing, a TEAE will be counted under the maximum severity possible.

- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

### 8.6.2. Clinical Laboratory Parameters

All clinical laboratory (clinical chemistry, hematology, urinalysis, coagulation, serology, and cytokines) parameters, with changes from baseline, will be listed; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables and boxplots by treatment and timepoint will be provided for clinical chemistry, hematology, serology, urinalysis, coagulation parameters and cytokines, with changes from baseline.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, calculation of summary statistics, and presentation in the figures, <x and ≤x values will be set to [0/half of x], whereas >x and ≥x values will be set to x.

### 8.6.3. Vital Signs Parameters

All vital signs parameters, with changes from baseline will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided for all vital signs parameters, with changes from baseline.

### 8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters, with changes from baseline, will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided for all 12-lead ECG parameters, with changes from baseline. An outlier analysis will be performed for QT interval corrected for heart rate using Bazett's formula (QTcB) and QT interval corrected for heart rate using Fridericia's formula (QTcF). The analysis will include all individual original, repeat, and unscheduled postdose values.

The maximum postdose values will be summarized by treatment according to the following categories:

- ≤450 ms
- >450 and ≤480 ms (all instances flagged in the listing)
- >480 and ≤500 ms (all instances flagged in the listing)
- >500 ms (all instances flagged in the listing)

The maximum increases from baseline will be summarized by treatment according to the following categories:

- ≤30 ms
- >30 and ≤60 ms (all instances flagged in the listing)
- >60 ms (all instances flagged in the listing)

### 8.6.5. Other Assessments

Medical history will be listed.

All other safety and tolerability assessments not detailed in the above sections will be listed only.

### 8.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

## 8.7. Immunogenicity Assessments

### 8.7.1. Immunogenicity Endpoints

The immunogenicity endpoints are anti-CPT31 antibodies, e.g., immunoglobulin (Ig)G, IgM. Immunogenicity samples will be collected on Day 1 predose, Day 2 (24 h), Day 5 (96 h) with an additional immunogenicity sample taken at the Follow-up visit.

### 8.7.2. Immunogenicity Statistical Methodology

All immunogenicity data will be listed.

The anti-CPT31 antibodies, e.g., immunoglobulin (Ig)G, IgM will be summarized.

Summary tables by treatment and timepoint will be provided for all immunogenicity data.

## 9. INTERIM ANALYSES

No formal interim statistical analyses are planned for this study.

## 10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

## 11. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

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5. Brown H, Prescott R. *Applied Mixed Models in Medicine*. Chichester: John Wiley & Sons, 1999.

6. Snedecor GW, Cochran WG. *Statistical Methods*. 8th ed. Ames, IA: Iowa State University Press, 1989.

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## 12. APPENDICES

### Appendix 1: Document History

| Status, Version | Date of Change | Summary/Reason for Changes |
|---|---|---|
| Final, Version 1.0 | NA | NA; the first version. |

NA = not applicable