**Title of study:** A Randomized, Double-blind, Placebo-controlled, First-in-human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers

**NCT Number:** NCT04392219

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**Date:** 30 June 2020

# Statistical Analysis Plan

## A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers

SAP Status: Final
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Protocol Reference: EIDD-2801-1001
Covance Study: 8427402

Sponsor:
Ridgeback Biotherapeutics
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Miami, FL 33133-5815
United States

Study Sites:
This study will be conducted at 1 site in the United Kingdom and up to 3 sites in the United States.

Principal Investigator:
[redacted]

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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 |
| AE | adverse event |
| $Ae_{t1-t2}$ | amount of the dose administered recovered in urine over the time interval t1 to t2 |
| ANOVA | analysis of variance |
| $AUC_{last}$ | the area under the plasma concentration-time curve, from time 0 to the last measurable non-zero concentration |
| $AUC_{0-inf}$ | the area under the plasma concentration-time curve from time 0 extrapolated to infinity |
| $AUC_{\tau}$ | area under the plasma concentration-time curve during a dosing interval hours postdose |
| $\%AUC_{extrap}$ | percentage of $AUC_{0-inf}$ that is due to extrapolation from the last quantifiable concentration to infinity |
| $\%AUC_{\tau, extrap}$ | percentage of $AUC_{\tau}$ that is due to extrapolation from the last quantifiable concentration to the end of the dosing interval |
| BLQ | below the limit of quantification |
| CDISC | Clinical Data Interchange Standards Consortium |
| CI | confidence interval |
| CL/F | apparent clearance following an extravascular dose |
| $CL_R$ | renal clearance |
| $C_{max}$ | maximum observed concentration |
| CSR | clinical study report |
| $C_{trough}$ | plasma concentration at the end of the dosing interval |
| CV | coefficient of variation |
| DMID | Division of Microbiology and Infectious Diseases |
| ECG | electrocardiogram |
| EOS | end of study |
| FDA | Food and Drug Administration |
| FE | food-effect |
| $Fe_{t1-t2}$ | percentage of the dose administered recovered in urine over the time interval t1 to t2 |
| FIH | first-in-human |
| GLSM | geometric least squares mean |
| ICH | International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ln | natural log |
| LSM | least squares mean |

| | |
|---|---|
| MAD | multiple ascending dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| $MR_{AUC}$ | EIDD-1931:EIDD-2801 ratio based on $AUC_{0\text{-}inf}$ |
| $MR_{Cmax}$ | EIDD-1931:EIDD-2801 ratio based on $C_{max}$ |
| MW | molecular weight |
| PBMC | peripheral blood mononuclear cells |
| PE | physical examination |
| [redacted] | [redacted] |
| PK | pharmacokinetic(s) |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| $RA_{AUC\tau}$ | observed accumulation ratio based on $AUC_{\tau}$ |
| $RA_{Cmax}$ | observed accumulation ratio based on $C_{max}$ |
| SAD | single ascending dose |
| SAP | statistical analysis plan |
| TEAE | treatment-emergent adverse event |
| TFL | table, figure, and listing |
| $t_{last}$ | time of the last quantifiable concentration |
| $t_{max}$ | time of the maximum observed concentration |
| $t_{1/2}$ | apparent terminal elimination half-life |
| $V_z/F$ | apparent volume of distribution during the terminal phase following and extravascular dose |
| WHODrug | World Health Organization Drug Dictionary |
| $\lambda_z$ | apparent terminal elimination rate constant |

# 1. INTRODUCTION

This SAP has been developed after review of the clinical study protocols (Final Version 5.1 (United Kingdom) dated 11 June 2020 and Final Version 5.2 (United States) dated 11 June 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 Ridgeback Biotherapeutics. 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 Ridgeback Biotherapeutics 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

## 2.1. Primary Objectives

The primary objective of Part 1 of the study is to determine the safety and tolerability of single ascending doses of EIDD-2801.

The primary objective of Part 2 of the study is to assess the effect of food on the PK on EIDD-2801 and EIDD-1931 following a single oral dose.

The primary objective of Part 3 of the study is to determine the safety and tolerability of multiple ascending doses of EIDD-2801.

## 2.2. Secondary Objectives

The secondary objectives of Part 1 and Part 3 of the study is to define the PK of EIDD-2801 and EIDD-1931 in plasma and urine following single and multiple doses administered to healthy volunteers.

The secondary objective of Part 2 of the study is to determine the safety and tolerability of single doses of EIDD-2801.

### 2.3. Exploratory Objectives

The exploratory objectives of Part 1 and of Part 3 are to collect data to assess the relationship between EIDD-2801/EIDD-1931 concentrations and QT interval corrected for heart rate (QTc).

## 3. STUDY ENDPOINTS

### 3.1. Primary Endpoints

The primary endpoints for Parts 1 and 3 of the study are results of safety evaluations including safety laboratory assessments, physical examinations (PEs), electrocardiograms (ECGs), vital signs, and adverse events (AEs).

The primary endpoints for Part 2 of the study are plasma PK parameters including $C_{max}$, $t_{max}$, $t_{1/2}$, CL/F, λz, Vz/F, $AUC_{0\text{-}inf}$ and $AUC_{last}$ as appropriate.

### 3.2. Secondary Endpoints

The secondary endpoints are as follows:

- Single-dose plasma PK parameters, including $C_{max}$, $t_{max}$, $t_{1/2}$, CL/F, λz, Vz/F, $AUC_{0\text{-}inf}$ and $AUC_{last}$ as appropriate (Part 1)
- Multiple-dose plasma PK parameters, including $C_{trough}$, $C_{max}$, $t_{max}$, $t_{1/2}$, CL/F, λz, Vz/F, $AUC_{\tau}$, $AUC_{0\text{-}inf}$ (Day 1 dose only), $RA_{AUC\tau}$ and $RA_{Cmax}$, as appropriate (Part 3)
- Urinary excretion of EIDD-2801 and EIDD-1931 following single- and multiple-dose administration (Parts 1 and 3).
- Results of safety evaluations including safety laboratory assessments, PEs, ECGs, vital signs, and AEs (Part 2).

## 4. STUDY DESIGN

### 4.1. Overview

EIDD-2801-1001 is a Phase 1, randomized, double-blind, placebo-controlled, first in human (FIH), single ascending dose (SAD), and multiple ascending dose (MAD) study of the safety, tolerability and PK of EIDD-2801 and EIDD-1931 following oral administration of single and multiple doses of EIDD-2801 to healthy volunteers. In addition, for a minimum of one cohort, the effect of food on the single-dose EIDD-2801 and EIDD-1931 PK parameters will be assessed in subjects taking open-label EIDD-2801. The overall objective of the study is to identify a starting dose for future safety and therapeutic intervention trials.

The study is composed of 3 parts; Part 1 is the SAD study, Part 2 is the FE cohort study, and Part 3 is the MAD study.

This study will be conducted at 1 site in the United Kingdom and up to 3 sites in the United States.

#### 4.1.1. Part 1 (Single Ascending Dose)

A single oral dose of EIDD-2801 or Placebo will be administered to subjects. Subjects will be randomized in a 3:1 ratio to receive either EIDD-2801 or Placebo.

Following dosing on Day 1, subjects will remain in the clinic through completion of study assessments on Day 4, returning to the clinic on Day 9 for study assessments, and Day 15 for the end of study (EOS) visit.

The first cohort will be divided into 2 groups. The first group, a sentinel group, will include 2 subjects. On Day 1, one subject in the sentinel group will be administered Placebo and one will be administered EIDD-2801. Analysis of the safety results for the sentinel group will be reviewed 24 hours postdose. If no halting criteria have been met, the remainder of the subjects in Cohort 1 (the second group) will be dosed. There will be no sentinel groups for the remaining cohorts.

After completion of each dosing cohort, safety and tolerability data will be reviewed to determine if any of the halting rules have been met. If not, then the subsequent cohort may be dosed following review of the 72-hour safety data. As PK data become available, these data may be used for dose-escalation decisions.

The proposed dose-escalation scheme is shown in

Figure 1, however, planned dose escalations will be determined based on ongoing review of the safety, tolerability, and available PK data. The starting dose in the first SAD cohort will be 50 mg. Dose levels will not increase by more than 3-fold for predicted nonpharmacologically active dose levels and by 2-fold for predicted pharmacologically active dose levels. The highest total daily dose to be studied under this protocol will not exceed 1600 mg.

Three cohorts are initially planned for Part 1; however, up to an additional 7 cohorts may be enrolled.

#### 4.1.2. Part 2 (Food-Effect)

Two single oral doses of EIDD-2801 will be administered to subjects, in an open-label manner. The dose for the Part 2/food-effect cohort is planned to be 100 mg but may be adjusted based on safety, tolerability, and/or PK data from Part 1. The dose assessed in the Part 2 cohort will have been given previously to subjects in a Part 1 cohort successfully (i.e., no halting rules were met following dosing).

Subjects will be randomized to a treatment sequence; i.e., to receive drug in the fed then fasted state (Sequence 1) versus fasted then fed state (Sequence 2;

Figure 1). Half of the subjects in the cohort will be randomized to Sequence 1 and the other half will be randomized to Sequence 2.

Following dosing on Day 1, subjects will remain in the clinic through completion of study assessments on Day 4, returning to the clinic on Day 9 for study assessments, and Day 14 to begin the second dosing sequence on Day 15. Subjects will then be discharged from the clinic on Day 18, returning to the clinic on Day 23 for study assessments, and Day 30 for the EOS visit. There will be a 14-day (minimum) washout period between doses.

One cohort of 10 subjects is planned for Part 2. However, if PK results obtained are equivocal, additional subjects may be enrolled into the Part 2/food-effect cohort at the previously tested dose or an additional Part 2/food-effect cohort may be added at a different dose.

#### 4.1.3. Part 3 (Multiple Ascending Dose)

Subjects in Part 3 will be randomized in a 3:1 ratio to receive either EIDD-2801 or Placebo. Twice-daily dosing will be administered to subjects on Day 1 through Day 5, inclusive, and a final dose will be administered on the morning of Day 6 for collection of steady-state PK samples during waking hours. Depending on ongoing review of the safety, tolerability, and PK data, the number of days of dosing may be reduced and the dosing frequency may be changed; the dosing frequency will be no less than once-daily or no greater than three-times daily.

The proposed dose-escalation scheme is shown in

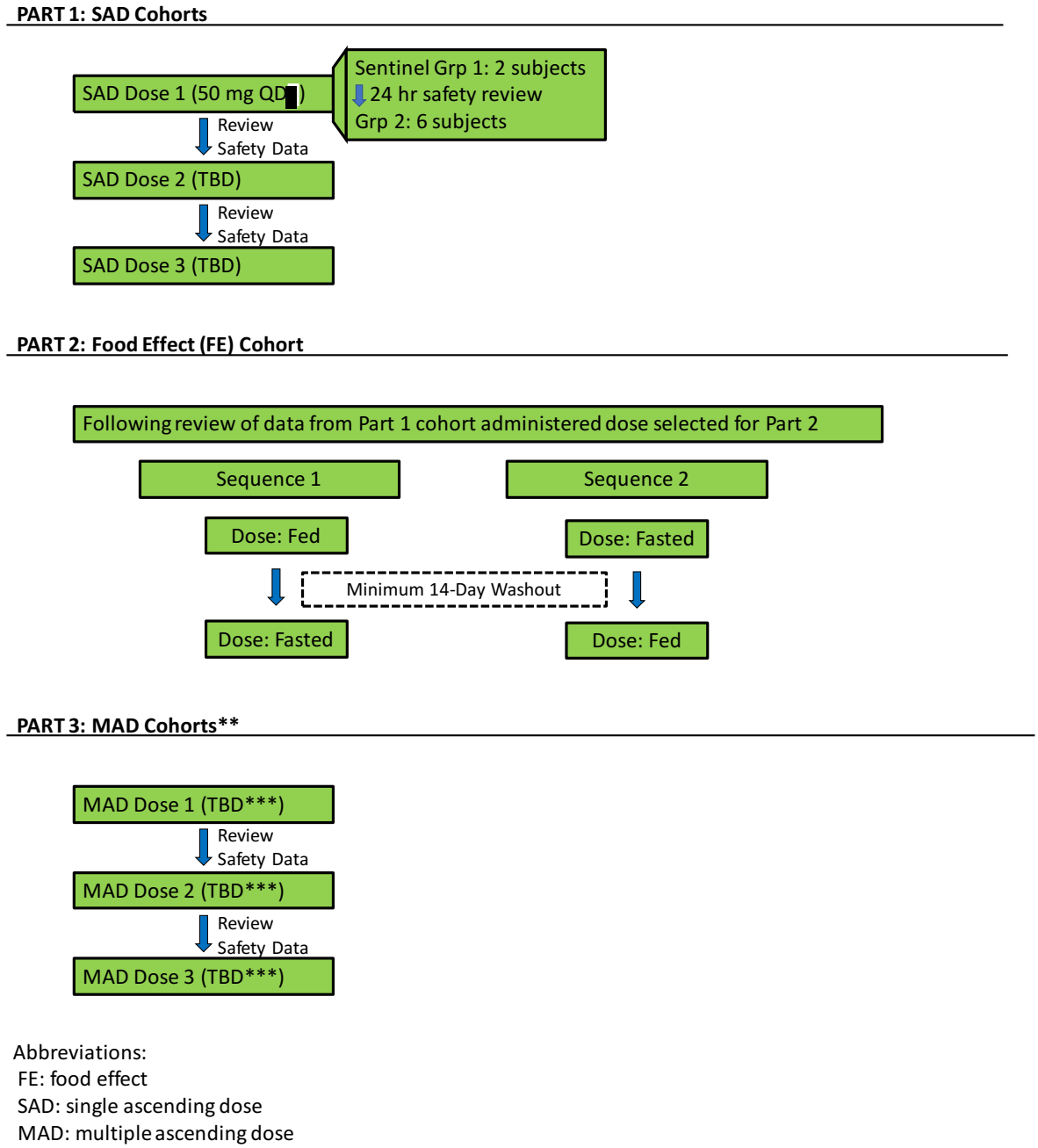
Figure 1. The total daily dose will not exceed a dose shown to be safe and well-tolerated in Part 1. Doses in Part 3 may be administered in the fed state, following review of the PK data obtained from Part 2. Part 3 may run in parallel with Part 1, providing that the total daily dose to be administered does not exceed a dose already shown to be safe and well-tolerated in Part 1.

Subjects will remain domiciled at the site during the dosing period and until Day 9, returning to the clinic on Day 14 for completion of study assessments, and Day 20 for the EOS visit. If the number of days of dosing are reduced, the timepoints for subsequent assessments and the period for which subjects are domiciled at the clinic will similarly be changed (subjects will be domiciled for 3 days post final dose).

Three cohorts are initially planned for Part 3; however, up to an additional 6 cohorts may be enrolled, or the number of cohorts may be reduced if the study objectives are met. Dose levels in Part 3 may be repeated for collection of peripheral blood mononuclear cells (PBMCs), providing that the dose level did not meet the dose-escalation halting criteria.

**Additional parts may be added to this study, including a SAD part in elderly healthy subjects and a study of the safety, tolerability, and PK in Japanese subjects. These additional parts may be added via a protocol amendment.**

**Figure 1: Study Design**




Abbreviations:
FE: food effect
SAD: single ascending dose
MAD: multiple ascending dose

[redacted]

*** Part 3 may run in parallel with Part 1, providing that the total daily dose to be administered does not exceed a dose already shown to be safe and well tolerated in Part 1*
****The total daily dose in Part 3 will not exceed a dose shown to be safe and well-tolerated in Part 1*

## 5. SAMPLE SIZE JUSTIFICATION

No formal sample size calculation was conducted. The sample size of 8 per cohort (6 active: 2 Placebo) for the SAD and MAD cohorts is considered adequate for a Phase 1 FIH

study. The sample size of 10 subjects (all administered EIDD-2801) is in accordance with Food and Drug Administration (FDA) guidelines for sample size in food-effect studies.

## 6. STUDY TREATMENTS

All treatments described are the planned treatments. The TFLs will reflect the actual treatments received, and dose levels will be displayed in increasing order where applicable. Screen failure subjects will have treatment 'Screen Failure' presented in all applicable listings.

### 6.1. Part 1

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

**Table 1: Presentation of Study Treatments in TFLs**

| Study Treatment | Order in TFLs |
|---|---|
| Placebo (fasted) | 1 |
| 50 mg EIDD-2801 [redacted] (fasted) | 2 |
| 100 mg EIDD-2801 [redacted] (fasted) | 3 |
| 200 mg EIDD-2801 [redacted] (fasted) | 4 |
| 400 mg EIDD-2801 [redacted] (fasted) | 5 |
| 600 mg EIDD-2801 [redacted] (fasted) | 6 |
| 800 mg EIDD-2801 [redacted] (fasted) | 7 |
| XXX mg EIDD-2801 [redacted] (fasted) | 8 |

[redacted]
Additional treatment labels may be added in the same format if additional cohorts are required. Amend the formulation as required as changes may occur throughout the study.
All Placebo groups will be pooled [redacted] for summaries but in the listings the formulation will be indicated in the treatment label as 'Placebo [redacted] (fasted)' or 'Placebo [redacted] (fasted)'.
As the capsule formulation is expected to be utilized for the latter cohorts, the [redacted] EIDD-2801 treatment groups will be summarized after the [redacted] EIDD-2801 treatment groups.

### 6.2. Part 2

The study treatment names, abbreviations, and ordering to be used in the TFLs are presented in Table 2.

**Table 2: Presentation of Study Treatments in TFLs**

| Study Treatment | Order in TFLs |
|---|---|
| 200 mg EIDD-2801 [redacted] (fasted) | 1 |
| 200 mg EIDD-2801 [redacted] (fed) | 2 |

Additional treatment labels may be added in the same format if additional cohorts are required. Amend the formulation as required as changes may occur throughout the study.

The study treatment sequence names, abbreviations, and ordering to be used in the TFLs are presented in Table 3.

**Table 3: Presentation of Study Treatment Sequences in TFLs**

| Study Treatment Sequence | Abbreviation | Order in TFLs |
|---|---|---|
| 200 mg EIDD-2801 [redacted] (fed) / 200 mg EIDD-2801 [redacted] (fasted) | 200 mg EIDD-2801 [redacted] (fed/fasted) | 1 |
| 200 mg EIDD-2801 [redacted] (fasted) / 200 mg EIDD-2801 [redacted] (fed) | 200 mg EIDD-2801 [redacted] (fasted/fed) | 2 |

Additional treatment sequences may be added in the same format if an additional cohort at a different dose level is required. Amend the formulation as required as changes may occur throughout the study.

### 6.3. Part 3

The study treatment names, abbreviations, and ordering to be used in the TFLs are presented in Table 4.

**Table 4: Presentation of Study Treatments in TFLs**

| Study Treatment | Order in TFLs |
|---|---|
| Placebo [redacted] BID (fasted) | 1 |
| 50 mg EIDD-2801 [redacted] BID (fasted) | 2 |
| 100 mg EIDD-2801 [redacted] BID (fasted) | 3 |
| 200 mg EIDD-2801 [redacted] BID (fasted) | 4 |
| 300 mg EIDD-2801 [redacted] BID (fasted) | 5 |
| 400 mg EIDD-2801 [redacted] BID (fasted) | 6 |
| XX mg EIDD-2801 [redacted] BID (fasted) | 7 |

Fasted in the treatment labels above indicates that subjects were fasted prior to the morning dose on PK Days 1 and 6. BID indicates twice daily dosing on Days 1 to 5 and single dose on Day 6. Additional treatment labels may be added in the same format if additional cohorts are required. Amend the frequency, formulation and dietary state as required as changes may occur throughout the study.

## 7. DEFINITIONS OF POPULATIONS

Any protocol deviations, including those related to COVID-19, 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 drug (EIDD-2801 or Placebo).

### 7.3. Pharmacokinetic Population

The PK population will include all subjects receiving study drug who comply sufficiently with protocol requirements (i.e., no major protocol violations) and for whom a sufficient number of analyzable PK samples (at least 1 quantifiable postdose sample) have been obtained to permit the determination of the PK profile for EIDD-2801/EIDD-1931 and the statistical analysis of the results. Subjects who experience an AE of vomiting before 2× the median $t_{max}$ of the group may be excluded from the PK population.

## 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 1.1 (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.

All protocol deviations and data issues (eg, missing data or data outside of the protocol windows) that occur during the study, including those related to COVID-19, will be considered prior to database lock for their severity/impact on how the data will be displayed and analysed statistically.

### 8.1.2. 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, with the exception of the ECG outlier analysis (see Section 8.6.4).

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 8.1.3) and ECG outlier analysis (see Section 8.6.4).

### 8.1.3. Definitions of Baseline, and Change from Baseline

The baseline will be defined as the last value recorded prior to dosing (Part 1)/dosing in each period (Part 2)/the first dose (Part 3). 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 (Part 1)/dosing in each period (Part 2)/the first dose (Part 3).

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 8.1.2 for more detail on handling repeat and unscheduled readings in the calculations.

### 8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by treatment (Part 1 and Part 3)/treatment sequence (Part 2) 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 (Part 1 and Part 3)/treatment sequence (Part 2) 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 (Part 1)/the first dose (Part 2 and Part 3). Concomitant medication will be defined as medication that starts during or after dosing (Part 1)/the first dose (Part 2 and Part 3) or starts but does not end prior to dosing (Part 1)/the first dose (Part 2 and Part 3).

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

PK parameters will be determined using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara, Version 8.1 or higher).

The following parameters will be calculated where possible from the plasma concentrations of EIDD-2801 and EIDD-1931:

| Parameter | Units[a] | Definition |
|---|---|---|
| $AUC_{last}$ | h*ng/mL | the area under the plasma concentration-time curve, from time 0 to the last measurable non-zero concentration[b], (Part 1, Part 2 and Part 3). |
| $AUC_{0\text{-}inf}$ | h*ng/mL | the area under the plasma concentration-time curve from time 0 extrapolated to infinity[b],[c]. (Part 1, Part 2, and Day 1 dose of Part 3). |
| $AUC_{\tau}$ | h*ng/mL | area under the plasma concentration-time curve during a dosing interval[b] (Part 3 only) |
| $\%AUC_{extrap}$ | % | percentage of $AUC_{0\text{-}inf}$ that is due to extrapolation from the last quantifiable concentration to infinity |

| | | |
|---|---|---|
| $\%AUC_{\tau, extrap}$ | % | percentage of $AUC_\tau$ that is due to extrapolation from the last quantifiable concentration to the end of the dosing interval |
| $C_{max}$ | ng/mL | maximum observed concentration |
| $t_{max}$ | h | time of the maximum observed concentration |
| $t_{last}$ | h | time of the last quantifiable concentration |
| $\lambda_z$ | 1/h | apparent terminal elimination rate constant |
| $t_{1/2}$ | h | apparent terminal elimination half-life |
| CL/F | L/h | apparent clearance following an extravascular dose (EIDD-2801 only) |
| $V_z/F$ | L | apparent volume of distribution during the terminal phase following and extravascular dose (EIDD-2801 only) |
| $C_{trough}$ | ng/mL | plasma concentration at the end of the dosing interval (Part 3 only) |
| $MR_{AUC}$ | | EIDD-1931:EIDD-2801 ratio based on $AUC_{0\text{-}inf}$ (Day 1) or $AUC_\tau$ (Part 3 only, Day 6) |
| $MR_{Cmax}$ | | EIDD-1931:EIDD-2801 ratio based on $C_{max}$ |
| $RA_{AUC\tau}$ | | observed accumulation ratio based on $AUC_\tau$ (Part 3 only). |
| $RA_{Cmax}$ | | observed accumulation ratio based on $C_{max}$ (Part 3 only). |

[a] Units are based on concentration units (provided by bioanalytical lab) and dose units used in the study.
[b] AUC will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
[c] Based on last observed quantifiable concentration

In addition, dose normalized parameters will be calculated for $AUC_{last}$, $AUC_{0\text{-}inf}$, $AUC_\tau$ and $C_{max}$, calculated by dividing the parameter by the administered dose in mg. These parameters will follow the same naming convention as the original parameter with the prefix 'D', eg, $DC_{max}$.

The following parameters will be where possible from the urine concentrations of EIDD-2801 and EIDD-1931:

| **Parameter** | **Units[a]** | **Definition** |
|---|---|---|
| $Ae_{t1\text{-}t2}$ | mg | amount of the dose administered recovered in urine over the time interval t1 to t2 (calculated by interval and cumulatively) |
| $Fe_{t1\text{-}t2}$ | % | percentage of the dose administered recovered in urine over the time interval t1 to t2 (calculated by interval and cumulatively) |
| $CL_R$ | L/h | renal clearance |

[a] Units are based on concentration units (provided by bioanalytical lab) and dose units used in the study.

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will, where possible, be carried out using actual blood sampling times postdose. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

Pharmacokinetic parameters will be derived where possible for all subjects. Data from subjects with incomplete profiles (missed blood draws, lost samples, samples unable to be quantified) may be used if PK parameters can be estimated using the remaining data points.

The following molecular weights (MW) will be used in calculations where required

EIDD-2801 329.31 g/mol

EIDD-1931 259.22 g/mol

$C_{max}$, $t_{last}$ and $t_{max}$ will be obtained directly from the concentration-time profiles. If $C_{max}$ occurs at more than 1 timepoint, $t_{max}$ will be assigned to the first occurrence of $C_{max}$.

Parent : prodrug ratios will be calculated as follows:

$$MR_{AUC} = (AUC_{0\text{-inf EIDD-1931}}/MW_{EIDD\text{-}1931} / (AUC_{0\text{-inf, EIDD-2081}}/MW_{EIDD\text{-}2801})$$

$$MR_{Cmax} = (C_{max,\ EIDD\text{-}1931}/MW_{EIDD\text{-}1931}) / (C_{max,\ EIDD\text{-}2801}/MW_{EIDD\text{-}2801})$$

$AUC_{last}$ or other common partial area may be used to determine $MR_{AUC}$ if $AUC_{0\text{-inf}}$ cannot be reliably calculated for the majority of subjects.

### 8.5.1.1. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-Life

The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in 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 |
|---|---|---|
| $\lambda_z$ | 1/h | apparent terminal elimination rate constant |
| $\lambda_z$ Upper | h | end of exponential fit |
| $\lambda_z$ Lower | h | start of exponential fit |
| $\lambda_z$ N | Not applicable | number of data points included in the log-linear regression |
| $\lambda_z$ Span Ratio | Not applicable | time period over which $\lambda_z$ was determined as a ratio of $t_{1/2}$ |
| $R^2$-adj | Not applicable | adjusted coefficient for determination of exponential fit |

Where possible, the span of time used in the determination of $\lambda_z$ (ie the difference between $\lambda_z$ Upper and $\lambda_z$ Lower) should be ≥2 half-lives. If the $\lambda_z$ Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the CSR.

### 8.5.1.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

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 >20%, $AUC_{0\text{-}inf}$ (and derived parameters) may be excluded from summary statistics and statistical analysis at the discretion of the sponsor or PK analyst.

If $AUC_{0\text{-}inf}$ cannot be determined reliably for all subjects and/or dose levels/treatments, an alternative AUC measure, such as AUC to a fixed timepoint or $AUC_{last}$, may be used in the statistical analysis.

### 8.5.1.3. Calculation of Urinary Parameters

The amount of drug excreted in urine (Ae) and urine collection interval ($t_1$-$t_2$) will be calculated as the product of urine analyte concentration and urine volume. Where only urine sample weight is supplied, a specific gravity of 1 g/mL will be assumed, and it will be considered equivalent to urine volume. A total cumulative $Ae_{0\text{-}x\ h}$ will be calculated by summing the $Ae_{t1\text{-}t2}$ values over the 0-x h interval, where x = end of the last collection time interval.

The percentage of the dose administered over the time interval t1 to t2 ($Fe_{t1\text{-}t2}$) as EIDD-2801 will be calculated for each urine collection interval as:

$$Fe_{t1\text{-}t2} = (Ae_{t1\text{-}t2} / Dose) \times 100\%.$$

The $Fe_{t1\text{-}t2}$ excreted as EIDD-1931 will be calculated for each urine collection interval as:

$$Fe_{t1\text{-}t2} = Ae_{t1\text{-}t2,\ EIDD\text{-}1931} / (Dose_{EIDD\text{-}2801} \times [MW_{EIDD\text{-}1931} / MW_{EIDD\text{-}2801}]) \times 100\%$$

Cumulative $Fe_{0\text{-}x\ h}$ will be calculated by summing the $Fe_{t1\text{-}t2}$ values over the 0-x h period in the same manner as $Ae_{0\text{-}x\ h}$.

Renal clearance will be calculated as follows:

$$CL_R = Ae/AUC$$

where both $A_e$ and AUC are determined over co-incident time ranges after dosing.

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

Plasma concentration values that are below the limit of quantification (BLQ) will be set to a value of zero, with the following defined exceptions which will be set to missing:

- Any embedded BLQ value (between 2 quantifiable concentrations).
- BLQ values following the last quantifiable concentration in a profile.

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.

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 a predose plasma concentration is missing, it may be set to zero by default.

Urine concentrations that are BLQ will be set to zero for the calculation of $Ae_{t1\text{-}t2}$.

#### 8.5.1.5. 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 prior to the first dose will be considered anomalous and set to missing for the PK analysis.

### 8.5.2. Presentation of Pharmacokinetic 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 summary statistics.

Individual concentrations that are deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For PK concentration data, $C_{max}$ and $C_{trough}$ the following rules will be applied:

- Values that are BLQ will be set to 0 for calculation of summary statistics.
- Arithmetic mean or median that are BLQ will be presented as 0.

For PK parameters the following rule will be applied:

- Geometric mean and coefficient of variation will not be calculated for $t_{max}$, and $t_{last}$.

### 8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables, mean 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.

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

### 8.5.3.1. Dose Proportionality

In Part 1 on day 1 a statistical analysis will be conducted to investigate the dose proportionality of the [redacted] formulation for PK parameters of EIDD-2801 and EIDD-1931 ($AUC_{0\text{-}inf}$, $AUC_{last}$, and $C_{max}$).

A statistical analysis will also be conducted to investigate the dose proportionality of the [redacted] formulation on day 1 for PK parameters of EIDD-2801 and EIDD-1931 ($AUC_{0\text{-}inf}$, $AUC_{last}$, and $C_{max}$) by combining the day 1 Part 3 data with the Part 1 [redacted] cohorts.

In Part 3 on day 6 a statistical analysis will be conducted to investigate the dose proportionality for PK parameters of EIDD-2801 and EIDD-1931 ($AUC_{\tau}$, and $C_{max}$). The dose proportionality assessments will include dose levels from a common dietary state.

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 90% confidence interval (CI), and between-subject coefficient of variation (CV) will be calculated. Figures (on the logarithmic scale) containing individual values, power model line (90% 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 90% CI for the slope spans 1.

In the case of lack of dose proportionality, between treatment pairwise comparisons based on ln-transformed dose normalized PK parameters will be performed using an analysis of variance (ANOVA) model.[5] The model will include dose as a factor. For each PK parameter separately, the least squares mean (LSM) for each dose, difference in LSMs between each

dose, and corresponding 90% CIs will be calculated; these values will then be back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90% CI.

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

**Power Model Analysis**

```
proc mixed data = <data in> alpha = 0.1;
 by parcat1n parcat1 pkday paramn param;
 model lpk = ldose / cl residual ddfm = kr2;
 ods output solutionf = <data out>;
run;
```

**Power Model Analysis (Between-subject Variability)**

```
proc mixed data = <data in> covtest alpha = 0.05;
 by parcat1n parcat1 pkday paramn param;
 class ldose;
 model lpk = ldose / cl residual ddfm = kr2;
 ods output covparms = <data out>;
run;
(Note: Pooled Geometric CV (%) = 100*(sqrt(exp(estimate)-1)))
```

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

```
proc mixed data = <data in>;
 by parcat1n parcat1 pkday paramn param;
 class dose;
 model lpk = ldose dose / htype = 1 ddfm = kr2;
 ods output tests1 = <data out>;
run;
```

**ANOVA Model Analysis**

```
proc mixed data = <data in> alpha = 0.1;
 by parcat1n parcat1 pkday paramn param;
 class dose;
 model ldnpk = dose / cl residual ddfm = kr2;
 lsmeans dose / cl pdiff alpha=0.1;
 ods output lsmeans = <data out>;
 ods output diffs = <data out>;
 ods output tests3 = <data out>;
run;
```

### 8.5.3.2. Food-Effect

For Part 2 a statistical analysis will be conducted to investigate the food-effect by comparing treatments EIDD-2801 (fed) to EIDD-2801 (fasted) for PK parameters of EIDD-2801 and EIDD-1931 ($AUC_{0\text{-inf}}$, $AUC_{last}$, and $C_{max}$). If an additional cohort is enrolled with a different dose level then that cohort will be analyzed in a separate model.

The natural log (ln)-transformed PK parameters will be analyzed using a mixed model.[6] The model will include planned treatment sequence, period, and actual treatment as fixed effects, and subject within planned treatment sequence as a random effect.

For each PK parameter separately, the least squares mean (LSM) for each treatment, difference in LSMs between the fed and fasted treatments, and corresponding 90% CIs will

be calculated; these values will then be back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90% CI.

Additionally, the pooled estimate (across all treatments) of the within-subject coefficient of variation (CV) will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

A statistical analysis using the Wilcoxon signed-rank test[7] will be conducted to investigate the food-effect on the treatment by comparing the fed treatment to the fasted treatment for $t_{max}$. The median for each treatment, Hodges-Lehmann estimate of the median difference between the fed and fasted treatments, and corresponding 90% CIs will be calculated.

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

**Mixed Model Analysis**

```
proc mixed data = <data in>;
 by parcat1n parcat1 pkday paramn param;
 class trtan aperiod trtseqp usubjid;
 model lpk = trtan aperiod trtseqp / cl residual ddfm = kr2;
 lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
 random intercept / subject = usubjid(trtseqp);
 ods output lsmeans = <data out>;
 ods output diffs = <data out>;
 ods output covparms = <data out>;
run;
```

**Wilcoxon Signed-rank Test**

```
proc univariate data = <data in> cipctldf(alpha = 0.1);
 by parcat1n parcat1 pkday paramn param;
 var ref test dif;
 ods output quantiles = <data out>;
 ods output testsforlocation = <data out>;
run;
(Note: Derive Hodges-Lehmann estimates)
```

### 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 Division of Microbiology and Infectious Diseases (DMID) toxicity scale (March 2014).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after dosing (Part 1)/the first dose (Part 2 and Part 3), or starts prior to dosing (Part 1)/the first dose (Part 2 and Part 3) and increases in severity after dosing (Part 1)/the first dose (Part 2 and Part 3).

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.

The assignment of TEAEs to treatments for Part 2 will be as follows:

- A TEAE occurring during or after Day 1 dosing and prior to Day 15 dosing will be assigned to the treatment given on Day 1 (period 1)
- A TEAE occurring during or after Day 15 dosing will be assigned to the treatment given on Day 15 (period 2)
- 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 (Part 1)/dosing in each period (Part 2)/the last dose (Part 3) 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, life-threatening, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, life-threatening, 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
- System organ class, preferred term, day of onset, and treatment (Part 3)

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 (Part 1)/the first dose (Part 2 and Part 3).
- 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 (Part 1) 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.

- If adverse events that change severity have a missing relationship, the relationship will be assigned to the same relationship as the original adverse event.

### 8.6.2. Clinical Laboratory Parameters

All clinical laboratory 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 chemistry, and hematology parameters, with changes from baseline.

Shifts from baseline tables will be provided for chemistry and hematology parameters.

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 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 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)

An extra listing presenting subjects with a QTcF>500 ms and/or an increase from baseline of >60 ms will be produced only if at least one occurrence of either of these criterion occur.

### 8.6.5. Other Assessments

All continuous ECG data in Part 1 and Part 3 will be archived without extraction or analysis and will not be reported in the scope of this study. The collection timepoints will be presented in a listing.

PBMCs may be collected from subjects in Part 3, depending upon ongoing review of the data. The collection of these samples may be omitted from some cohorts, depending on ongoing review of the data. The PBMCs will be stored for analysis of EIDD-2061 levels at some point in the future.

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.

## 9. INTERIM ANALYSES

No formal interim analyses are planned for this study. Data from Part 1 cohorts may be locked, unblinded, and analyzed prior to Part 2 and Part 3. Where applicable, doses will be

administered in an escalating manner following satisfactory review by the Sponsor and PI of the blinded safety and tolerability data.

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

EIDD-2801 concentration data were not quantifiable in some treatment groups and therefore PK parameters were not calculable. These affected groups will not have any parameter data presented and any analysis based upon these parameters will not be performed. Where limited samples were quantifiable (i.e. not a minimum of 3 consecutive concentrations with at least one after $C_{max}$) $C_{max}$ and $t_{max}$ may be reported.

The protocol indicated that the DMID toxicity grading scale would be used to grade laboratory parameters after taking into consideration institutional normal parameter ranges. The decision was made to evaluate out of reference laboratory parameters in the CSR only rather than using the DMID grading, as for several parameters the reference ranges used at the site were not consistent with the toxicity grading table provided in the protocol. Therefore, treatment-emergent toxicities based on DMID grading will not be reported and shift tables will be reported instead.

## 11. REFERENCES

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

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

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

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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. |
| Final, Version 2.0 | 30JUN2020 | Protocol amendment changes including:<br>● The total daily dose to be administered was increased to 1600 mg.<br>● The number of additional cohorts in Part 1 was increased to 7.<br>● The number of additional cohorts in Part 3 was increased to 6.<br>● Continuous 12-lead ECG monitoring was added in Part 1.<br>Updated due to awareness of further information during the conduct of the study:<br>● Known dose levels were added to the treatment labels and treatment clarifications were added.<br>● As the latter cohorts in Part 1 will use the [redacted] rather than [redacted] formulation the dose proportionality analysis section was updated to specify the dose proportionality assessments will be formulation specific and an additional assessment of dose proportionality for the [redacted] formulation will be performed by combining Part 1 [redacted] cohorts with Part 3 day 1 data.<br>● Changes to planned analysis section to reflect that certain PK parameter data may not be presented or analyzed and that DMID grading for laboratory data will not be performed.<br>● In the TFL Shells the screen failure subject data is presented in separate listings as there is no distinction during data collection which part a subject screen failed from.<br>● In the TFL Shells presenting important protocol deviations and any deviations related to COVID-19.<br>Minor formatting changes |

NA = not applicable

# Statistical Analysis Plan Approval Form

| | |
|---|---|
| **Sponsor Name:** | Ridgeback Biotherapeutics |
| **Sponsor Protocol ID:** | EIDD-2801-1001 |
| **Covance Study ID:** | 8427402 |
| **SAP Text Filename:** | EIDD-2801-1001_SAP_Final2.0 |
| **TFL Shells Filename:** | EIDD-2801-1001_TFL_Shells_Final2.0 |
| **Version:** | 2.0 |
| **Date:** | 30JUN2020 |

**Covance Approval(s):**

[redacted] 01JUL2020
Date

[redacted]
Printed Name/Title - Statistician, Qualifications

[redacted] 01JUL2020
Date

[redacted]
Printed Name/Title - Statistician, Qualifications

[redacted] 01 JUL 2020
Signature Date

[redacted]
Printed Name/Title - Pharmacokineticist, Qualifications

**Sponsor Approval:**

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study; and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based on this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

[redacted] 6/30/2020
Signature Date

[redacted] Chief Medical Officer
Printed Name/Title

Please scan/email completed form(s) to the Lead Statistician listed below:

| | |
|---|---|
| **Printed Name/Title:** | [redacted] |
| **Email:** | |



[redacted] ADDED MISSING JOB TITLE, JOB TITLE WAS CONFIRMED TO MATCH SIGN OFF ON THE V1.0 APPROVAL FORM