Statistical Analysis Plan J5B-MC-FHAD V1

A Phase 1, Single-Center, Open-Label, 2-Cohort, Fixed-Sequence, Drug-Drug Interaction Study to Assess the Pharmacokinetics of DC-806 When Orally Administered Alone, When Coadministered with Itraconazole, and When Coadministered with Carbamazepine in Healthy Adult Participants

NCT05994807

Approval Date: 13-Oct-2023

Statistical Analysis Plan

Sponsor:	DICE Therapeutics, Inc., A wholly owned subsidiary of Eli Lilly and Company
Protocol Number:	DCE806103
Protocol Title:	A PHASE 1, SINGLE-CENTER, OPEN-LABEL, 2-COHORT, FIXED-SEQUENCE, DRUG-DRUG INTERACTION STUDY TO ASSESS THE PHARMACOKINETICS OF DC-806 WHEN ORALLY ADMINISTERED ALONE, WHEN COADMINISTERED WITH ITRACONAZOLE, AND WHEN COADMINISTERED WITH CARBAMAZEPINE IN HEALTHY ADULT PARTICIPANTS
ICON Project Identifier:	DITBEE42-0D1NX7
SAP Version Date:	13-Oct-2023

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Biostatistician/Title:	PPD / Sr. Biostatistician
Signature of Biostatistician /Date:	PPD PPD 16 Oct 2023 17:53:04 UTC (Z) REASON: I approve this document as designee 31cb7c4b-460a-443a-adfb-361d637e6c9e
Name of Sponsor Representative /Title:	PPD / Director of Biostatistics
Signature of Sponsor Representative /Date:	PPD PPD 16 Oct 2023 18:48:04 UTC (Z) REASON: I approve this document e601950e-329c-40ed-8656-1911b52a9c4e

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3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under DICE Therapeutics, Inc. Protocol DCE806103.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 11-Aug-2023 (including all amendments up to this protocol date) and the eCRF version DCE806103 Version 1.0 dated 14-Aug-2023.

An approved and signed SAP is a requirement for database lock.

This SAP only covers the results that will be processed by the ICON Early Clinical and Bioanalytical (IEB) Biostatistics Department.

ICON IEB will perform the pharmacokinetic (PK) and safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified in this SAP. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes to Analysis

4.1 Changes from Protocol

There are no changes from the protocol.

4.2 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

5.1 Primary

To assess the effect of a CYP3A4 inhibitor (itraconazole) and CYP3A4 inducer (carbamazepine) on the single dose PK of DC-806 coadministered with itraconazole or carbamazepine in healthy male and female participants.

5.1.1 Primary Endpoints

Plasma PK parameters of DC-806: C_{max}, AUC_{0-t}, and AUC_{0-inf}, after dosed alone versus when coadministered with itraconazole or carbamazepine.

5.2 Secondary

To evaluate the safety and tolerability of DC-806 in the absence and presence of a CYP3A4 inhibitor (itraconazole), and a CYP3A4 inducer (carbamazepine) in healthy male and female participants.

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5.2.1 Secondary Endpoints

- Incidence of AEs
- Change from baseline in clinical laboratory, vital signs, physical examination findings, 12-lead ECG

5.3 Exploratory

- CCI
- CCI

5.3.1 Exploratory Endpoints

- CCI

6.0 Study Design

This is a Phase 1, single-center, open-label, 2-cohort, fixed-sequence, drug-drug interaction (DDI) study in up to 32 healthy male and female participants (up to CCI participants per cohort) to assess the effect of multiple doses of a CYP3A4 enzyme inhibitor (itraconazole) and of a CYP3A4 enzyme inducer (carbamazepine) on the single dose pharmacokinetics (PK) of DC-806.

This study will consist of 2 cohorts, with DC-806 serving as the victim drug in each cohort. Each study cohort will consist of 3 periods.

The following treatments will be administered:

Cohort 1 (n=CCI

Period 1:	A single oral dose of CCI mg DC-806 on Day 1 under fasted conditions
Period 2:	Multiple oral doses of once daily (QD) CCI mg itraconazole (CCI mg capsules) for 3 days (Day 4 to Day 6) under fed conditions
Period 3:	A single oral dose of CCI mg DC-806 will be administered 2 hours after a single oral dose of CCI mg itraconazole (CCI mg capsules) under fasted conditions, in the morning on Day 7. QD dosing of itraconazole (CCI mg) will continue until Day 10 under fed conditions

Cohort 2 (n=CCI

Period 1:	A single oral dose of CCI mg DC-806 on Day 1 under fasted conditions
Period 2:	Multiple-ascending oral doses of twice daily (BID) carbamazepine, under fed conditions, as follows: ▪ Day 4 to Day 5: BID doses of CCI mg carbamazepine ▪ Day 6 to Day 7: BID doses of CCI mg carbamazepine ▪ Day 8 to Day 17: BID doses of CCI mg carbamazepine (CCI mg + CCI mg tablets)
Period 3:	On Day 18, morning dosing: a single oral dose of CCI mg DC-806 will be coadministered with CCI mg carbamazepine (CCI mg + CCI mg tablets) under fasted conditions. Evening dosing: a single oral dose of CCI mg carbamazepine (CCI mg + CCI mg tablets) will be administered under fed conditions. BID administration of CCI mg carbamazepine will continue until Day 20, followed by down-titration until Day 24:

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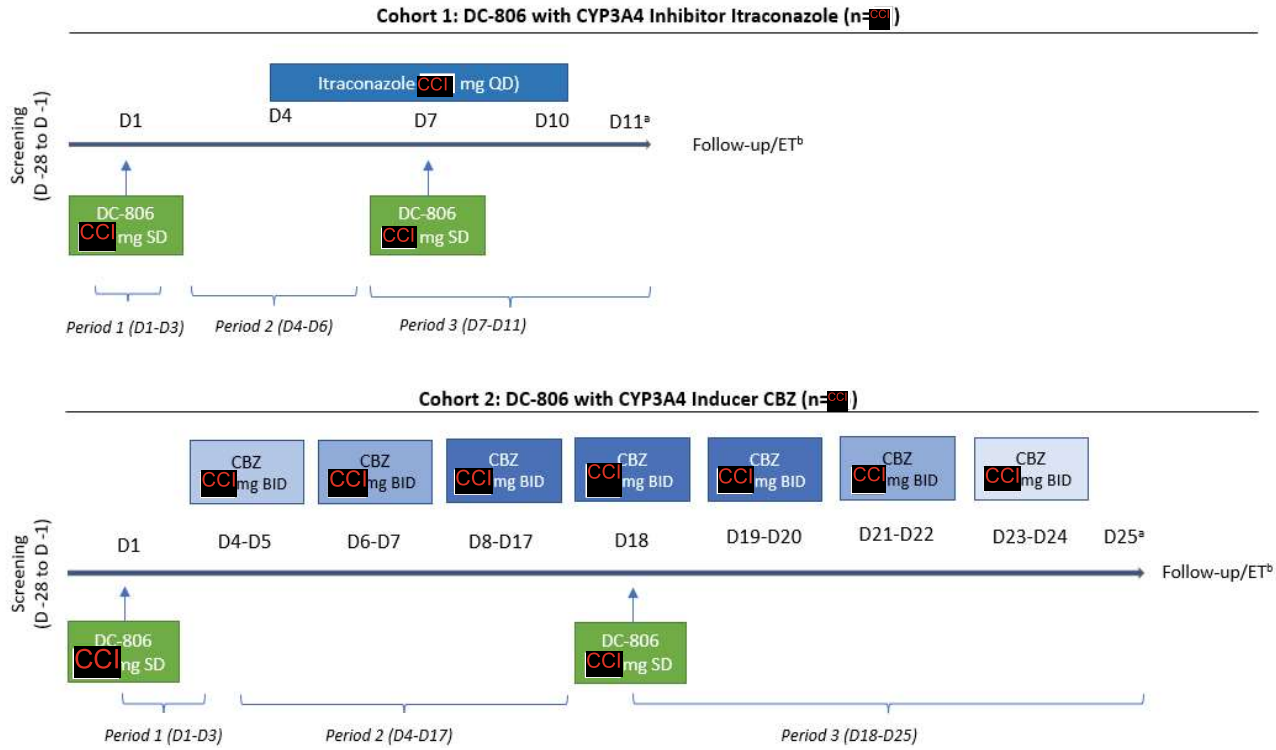
- Day 21 to Day 22: BID doses of CCI mg carbamazepine, under fed conditions
- Day 23 to Day 24: BID doses of CCI mg carbamazepine, under fed conditions

The study consists of an eligibility screening period of 28 days. The 3 treatment periods will involve the administration of a single dose of DC-806 alone and a single dose of DC-806 with multiple doses of itraconazole (Cohort 1, 11 days), and the administration of single dose of DC-806 alone and a single dose of DC-806 with multiple doses of carbamazepine (Cohort 2, 25 days). During the treatment periods, assessments will be performed for safety and PK with blood sampling for PK purposes up to 96 hours after DC-806 administration. Participants will be discharged on Day 11 (Cohort 1) and on Day 25 (Cohort 2), after completion of assessments.

Finally, a follow-up visit will be performed 10 (±2) days after the last dose of itraconazole (Cohort 1) and 6 (+2) days after the last dose of carbamazepine (Cohort 2), or at early termination (ET).

A diagram of the study design is presented in Figure 1.

Figure 1 Study Schema



BID=twice daily (morning and evening); CBZ=carbamazepine; CYP=cytochrome P450; D=day; ET=early termination; n=number of participants;

SD=single dose; QD=once daily.

[a]Participants will be discharged on Day 11 (Cohort 1) and on Day 25 (Cohort 2), after completion of assessments;

[b]Follow-up: 10 (±2) days after the last dose of itraconazole (Cohort 1), and 6 (+2) days after the last dose of carbamazepine (Cohort 2), or at ET.

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Study Schedule	
Screening	Between Day -28 and Day -1 (admission).
Treatment period	**Cohort 1 (itraconazole, CYP3A4 inhibitor)** Participants will be admitted to the clinical site on Day −1, which is the day prior to Day 1, the day of the first drug administration. Participants will be discharged on Day 11 after completion of all assessments. **Cohort 2 (carbamazepine, CYP3A4 inducer)** Participants will be admitted to the clinical site on Day −1, which is the day prior to Day 1, the day of the first drug administration. Participants will be discharged on Day 25 after completion of all assessments.
Follow-up/ET	10 (±2) days after the last dose of itraconazole (Cohort 1), and 6 (+2) days after the last dose of carbamazepine (Cohort 2), or at ET.

6.1 Sample Size Considerations

A total of approximately 32 healthy male and female participants will be enrolled in the study with up to [CCI] to be enrolled in each cohort, aiming to have approximately [CCI] evaluable participants per cohort assuming a [CCI]% drop out. For this study, no formal sample size calculation was done, because the extent of the potential interaction effect is unknown. The sample size of 32 participants (up to [CCI] per cohort) has been selected to provide adequate information on the effect of multiple doses of itraconazole and carbamazepine on the PK of DC-806.

6.2 Randomization and Blinding

This is an open-label, single-sequence study; no randomization or blinding will be conducted.

7.0 Overview of Planned TFL Deliveries

7.1 Pre-lock TFL

There will be 1 run of TFLs produced after database freeze and prior to lock. This draft of the safety TFLs (excluding PK) will be provided prior to database lock to assist in review of the database. As a result of draft TFLs review comments; revisions will be included in the post-lock TFL delivery.

Comments affecting the database will be provided to Data Management for resolution prior to database lock.

7.2 Final Analysis

Draft TFLs will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be finalized and provided to ICON Medical Writing for incorporation in the first draft CSR.

8.0 Definitions and General Analysis Methods

8.1 General Data Handling

8.1.1 Rounding

8.1.1.1 Listings

In listings collected data (from CRF or external source) will be presented with the same precision as the original data as entered or received. Derived data will be rounded for presentation purposes.

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8.1.1.2 Summary Tables

8.1.1.2.1 General Tables

The following will be rounded regardless of data type

Percentages (including %CV)	Geometric Mean Ratios and associated CIs
1 decimal place	3 decimal places

8.1.1.2.2 General Data

The following summary statistics will be rounded relative to the number of decimal places collected.

Statistic	Mean/Median	Standard Deviation	Minimum/ Maximum
# of decimal places in addition to that collected in data	+1 decimal place	+2 decimal places	+0 decimal places

The above rule can be applied directly to collected data. For derived data rounding will occur prior to summarization (in the derived dataset as determined by the statistician) so a specific number of decimal places will have to be assumed to apply the above rounding rules for summary statistics. For data with inconsistent number of decimals in raw data the most frequently occurring numbers of decimals will be used unless that number is large and causes difficulties in presentation in which case it will be trimmed to a presentable number (2-3 decimals).

8.1.1.2.3 Pharmacokinetic Tables

Pharmacokinetic concentration data is generally recorded to 3 significant digits. Based on this convention the following parameters will have summary statistics will be presented to the following number of significant digits. If recorded to a different precision these parameters will have the same precision as the data.

Parameter	**AUC, C_{max}, CL/F, Vz/F**
Statistic	**Mean/Median, Standard Deviation, Minimum/ Maximum, Geo mean**
Precision	3 significant digits

Pharmacokinetic time data is recorded on the CRF and pharmacokinetic time parameters will be rounded based on collection.

Parameter	**t_{max}, $T_{1/2}$**		
Statistic	Mean/Median	Standard Deviation	Minimum/ Maximum
# of decimal places	3 decimal places	4 decimal places	2 decimal places

8.1.2 Imputation

Unless otherwise noted, data will not be imputed.

8.1.3 Daylight Savings Time Adjustments

The clinic dates of the study are not expected to fall over Daylight Savings Time and no adjustments for time change are planned.

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8.1.4 General Descriptive Statistics

Continuous variables will be summarized with the following descriptive statistics and nomenclature: n = number of observations or participants, mean = arithmetic mean, SD = standard deviation, Min = minimum value, median = median value, and Max = maximum value.

Categorical variables will be summarized and presented with the following nomenclature: n = frequency and % = percentage. Percentages by categories will be based on the number of participants exposed within a treatment. The categories will be presented in the tables exactly as they appear in the case report form (CRF) / Database. Categories of NOT REPORTED, MISSING, and/or UNKNOWN may be excluded from summaries if null (0).Specific data types may include additional descriptive statistics or exclude some noted above. Any deviations from the general set of descriptive statistics will be noted in the sections related to the analysis of that data.

Data summarized in tables will have an associated listing. Data listed but not summarized will be noted in specific data type sections.

8.1.5 Pooling

No data pooling across treatments/cohorts.

8.1.6 Unscheduled Measurements

Unscheduled and early termination measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled and early termination measurements will be excluded from the descriptive statistics and statistical analysis.

8.2 Common Variable Definitions

8.2.1 Baseline Definition

Unless otherwise stated, baseline for postdose evaluations within each period is defined as the last observation recorded before the first study drug administration in each period. The last observation can be an unscheduled/repeated measurement. If a pre-treatment observation is missing in a given period then the screening value may be used.

For TFLs with triplicate ECG measurements the average of the triplicate measurements taken at pre-dose in each period are taken as baseline value, and the average of the triplicate measurements at 1 hour postdose in each period are taken as the 1 hour postdose value. For ECG shift table, the best clinical interpretation from the set of triplicate ECG measurements per timepoint will be used for categorizing ECG at predose, and the worst clinical interpretation will be used for categorizing ECG at postdose.

8.2.2 Treatment/Participant Grouping

The following grouping variables for treatments will be used as column headers in the TFLs.

Label	Grouping
Study Drugs	DC-806, Itraconazole, Carbamazepine
Treatments	Cohort 1 DC-806/ Itraconazole • DC-806 • DC-806 + Itraconazole Cohort 2 DC-806/ Carbamazepine • DC-806

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Label	Grouping
	• DC-806 + Carbamazepine
Dose Level	Cohort 1 DC-806/ Itraconazole • CCI mg DC-806, single dose • CCI mg Itraconazole (CCI capsules) QD Cohort 2 DC-806/ Carbamazepine • CCI mg DC-806, single dose • CCI mg Carbamazepine (CCI mg tablet) BID, CCI mg (CCI mg tablet) Carbamazepine BID, and CCI mg Carbamazepine CCI mg tablet + CCI mg tablet) BID

8.2.3 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 1.1 and Implementation Guide (ADaMIG) 1.2.

ADaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata and Analysis Data Reviewer's Guide (ADRG) will be included. Analysis results (analysis displays or program details) metadata (ARM) are excluded from the define.xml.

8.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® (WNL) version 8 or higher (Certara, L.P.). Additional PK computations may be performed in SAS®.

8.4 Statistical Methods

8.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

8.4.2 Hypothesis Testing

No formal hypothesis testing will be done.

8.5 TFL Layout

The layout of TFLs will be according to the ICON IEB standards.

TFL shells are provided with and approved as part of this SAP. Small changes to shell layout due to the nature of the data may be required after lock at the discretion of the ICON Biostatistician. Other changes to the shells may be out of scope. The TFLs will be provided as a single document in Adobe PDF format (in Letter), and as individual files for each table, figure and listing in Rich Text Format (.rtf).

9.0 Analysis Sets

The following subject level Analysis Sets (populations) will be used for summaries in the study.

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9.1 Enrolled Set

The Enrolled Set will consist of participants who signed informed consent and are represented in the database.

9.2 Safety Set

The Safety Set will consist of participants who receive any amount of DC-806, itraconazole, or carbamazepine. This set will be used for the safety data summaries, baseline characteristic summaries, and PK concentration summaries. This set will be analyzed as treated.

9.3 Pharmacokinetic Set

All participants who have received at least 1 dose of DC-806 and provided sufficient bioanalytical assessment results to calculate reliable estimates of the DC-806 PK parameters. This set will be used for the PK parameter summaries and primary analysis. This set will be analyzed as treated.

10.0 Demographic Data

10.1 Participant Disposition

The number of participants enrolled, and number and percentage of members of the Safety and PK analysis sets will be presented, by cohort and overall. The number and percentage of participants who completed, and the percentage of participants who withdrew from the study prematurely, and a breakdown of the corresponding reasons for treatment and study withdrawal will also be presented.

10.2 Protocol Deviations

Protocol deviations will be collected and reported per ICON's Protocol Deviation Management Standard Operating Procedure (SOP) and relevant Work Instruction (WI). Participant-level deviations will be extracted and pulled into the study tabulation model (SDTM) dataset from ICON's Clinical Trial Management System (CTMS). Deviations that have been reported and coded as "Important" will be listed by participant.

10.3 Demographics

Participant demographics at screening will be summarized by cohort and overall. The summary will include the participants' age (years), sex, race, ethnicity, weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Demographics will be summarized for the Safety Set and PK Set.

10.4 Medical History

Medical history, categorized by preferred term according to MedDRA Version 26.0, will be listed by participant.

10.5 Participant Characteristics

Baseline laboratory measurements including drug screen, pregnancy test, and any COVID Test Results will be listed.

10.6 Prior and Concomitant Medications

Prior and concomitant medications collected on the eCRF as defined by the protocol will be categorized by medication group and subgroup according to WHO Drug Dictionary. All concomitant medications will be listed by participant. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be noted in the listing. If the end date (e.g. partial or missing date) does not confirm that the medication was stopped prior to first DC-806 dose, the medication will not be flagged as prior.

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10.7 Treatment Compliance and Exposure

The number of participants receiving each dose of study drug per visit day will be summarized by cohort.

11.0 Pharmacokinetic Data

11.1 Pharmacokinetic Variables

Concentrations of DC-806 CCI will be collected in plasma.

PK parameters of DC-806 CCI will be calculated for plasma. A full list and definitions of parameters can be found in Appendix 2.

11.2 Plasma Pharmacokinetic Summaries

11.2.1 Plasma Concentrations

Plasma concentrations for DC-806 CCI below the quantifiable limit (BQL) will be set to 0 in the computation of descriptive statistics. Descriptive statistics (number of participants, mean, geometric mean, SD, coefficient of variation [%CV], median, min, max, and number of BQL observations) will be used to summarize the plasma concentrations by cohort and treatment at each scheduled timepoint. Separate tables will be presented for each cohort.

Linear (±SD) and semi-logarithmic (+SD) plots of the arithmetic mean plasma concentration by scheduled sampling time will be provided by treatment. These plots will show time in hours (in a real time scale). The plots will present all calculated means and linear plots will include a reference line for the lower limit of quantification (LLOQ). The mean concentrations for DC-806 and DC-806 in combination with either itraconazole or DC-806 in combination with carbamazepine will be presented on each plot.

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by participant (one participant per page). These plots will show time in hours. Individual plots will use the BQL handling procedure described below for “Plasma Pharmacokinetic Parameters”, and linear plots will include a reference line for the lower limit of quantification. In addition, spaghetti plots of individual concentrations will be presented, with all participants in a given treatment condition per plot (linear and semi-log plots).

11.2.2 Plasma Pharmacokinetic Parameters

11.2.2.1 Calculation and Summary of PK Parameters

Plasma PK parameters for DC-806 CCI will be estimated using non-compartmental methods with WinNonlin® using best fit regression. The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using linear up/log down method. In estimating the PK parameters, BQL values will be set to zero. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time is missing, the scheduled time will be substituted and flagged.

A table of descriptive statistics (number of participants, mean, geometric mean, SD, %CV, median, min, and max) will be used to summarize the calculated PK parameters by cohort and treatment. For t_{max}, only median, min and max will be presented.

A scatter plot of individual (plus mean and median) PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} by cohort and treatment for each analyte will be provided.

Box-and-whisker plots of plasma pharmacokinetic parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) will also be provided for each cohort (with parameters for DC-806 and DC-806 in combination with either itraconazole or DC-806 in combination with carbamazepine presented on each plot).

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Finally, scatter plots of individual plasma pharmacokinetic parameters will be presented by cohort (with datapoints for individual values, as well as the mean and median for each treatment).

The following flags will be used to exclude parameters that meet the predefined exclusion criteria for summary and analysis.

Criteria Name	Exclusion Criteria	Parameters to be Evaluated using the Exclusion Criteria
Extrapolation	AUC%Extrap > 20%	$AUC_{0\text{-}inf}$, CL/F, Vz/F
Regression	Adj Rsq < 0.8	$AUC_{0\text{-}inf}$, $T_{1/2}$, CL/F, Vz/F
Span	Span <= 2	$AUC_{0\text{-}inf}$, $T_{1/2}$, CL/F, Vz/F

Note: Flags will be applied to parameters prior to derivation of additional parameters in SAS and will be used to exclude derived parameters as well.

All parameters will be listed by participant, and parameters that meet the exclusion criteria will be accompanied by an indication of criteria met. Additionally the ratios of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} for DC-806 with and without either itraconazole or carbamazepine will be listed.

Diagnostic parameters are listed but not summarized.

11.2.2.2 Statistical Analysis of PK parameters

The effect of itraconazole and carbamazepine on the PK of DC-806 will be assessed using the geometric least-squares (LS) mean ratio (GMR) and CCI % confidence intervals of GMR of the primary plasma PK parameters: C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ for DC-806. These values will be estimated from a linear mixed model on the natural log-transformed value of the parameter including a fixed effect for treatment and a random effect for participant. Separate models will be performed for itraconazole and carbamazepine. Estimates on the original scale of measurement will be obtained by exponentiating point estimates on the natural log scale. Geometric LS means will be provided for each treatment. In all comparisons, DC-806 administered alone will be used as the reference. No adjustments will be made for multiplicity.

A summary table for each cohort will present the number of observations and exponentiated LS means for each treatment along with the geometric LS mean ratio and CCI % confidence interval.

12.0 Pharmacogenomic Data

Potential drug metabolizing enzymes and transporter(s) genetic variants are outside of the scope of this SAP.

13.0 Safety Data

13.1 Adverse Events (AEs)

Treatment-emergent adverse events (TEAEs) are those that occur or worsen after the first dose of study drug.

For Cohort 1, TEAEs occurring following dosing on Day 1 but before dosing on Day 4 will be counted under treatment with DC-806. TEAEs occurring following dosing on Day 4 but before dosing on Day 7 will be counted under treatment with itraconazole alone. TEAEs occurring following dosing on Day 7 will be counted under treatment with DC-806 coadministered with itraconazole. Cohort 1 AE summary tables will be presented by treatment (DC-806, itraconazole, DC-806 + itraconazole) and overall.

For Cohort 2, TEAEs occurring following dosing on Day 1 but before dosing on Day 4 will be counted under treatment with DC-806. TEAEs occurring following dosing on Day 4 but before dosing on Day 18 will be counted under treatment with carbamazepine alone. TEAEs occurring following dosing on Day 18 will be

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counted under treatment with DC-806 coadministered with carbamazepine. Cohort 2 AE summary tables will be presented by treatment (DC-806, carbamazepine, DC-806 + carbamazepine) and overall.

The following missing data will be imputed as defined (for calculations/summary tables only and will not be presented in listings):

Missing Data Point	Imputation Purpose	Derivation Description
Start Time	Calculation of Onset/Duration	Start Time=00:01
End time	Calculation of Onset/Duration	End Time=23:59
Severity	Summary Display	Severity =Missing
Relationship	Summary Display	Relationship =Missing
Start Time on dosing day	TEAE determination	TEAE=Y
Start Time on dosing day	Treatment Assignment	Treatment=treatment given on dosing day
Start Date	TEAE determination	TEAE=Y
Start Date	Treatment Assignment	Treatment=Missing

A table summarizing the total number of TEAEs, number and percentage of participants reporting at least one TEAE, categorization of number and percentage of participants with at least one TEAE by most severe and most drug related event, total number of serious AEs (SAEs), total number of participants with at least one SAE, and total number of participants who discontinued study drug due to an AE will be provided.

A summary of the number and percentage of participants reporting each TEAE and number of TEAEs, categorized by system organ class and preferred term coded according to the MedDRA, will be presented by treatment and overall. For counting by participant, participants will only be counted once within each body system or preferred term.

A summary of the number and percentage of participants reporting each TEAE and number of TEAEs will be presented by relationship to study drug (NOT RELATED and UNLIKELY RELATED = Not Related, POSSIBLY RELATED and RELATED=Related) by treatment and overall. Participants with multiple events within a system organ class or preferred term will be counted under the category of their most drug-related event within that system organ class and/or preferred term.

A summary of the number and percentage of participants reporting each TEAE and number of TEAEs will be presented by severity (as recorded on the eCRF) by treatment and overall. Participants with multiple events within a system organ class or preferred term will be counted under the category of their most severe event within that system organ class or preferred term.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed by participant.

A separate listing of AEs leading to study drug discontinuation will be provided.

13.2 Deaths and Serious Adverse Events (SAEs)

A listing of deaths and other SAEs will be provided by participant.

13.3 Laboratory Data

Clinical laboratory data will be presented using standardized units, conversions will be applied to the data received from the laboratory.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology, urinalysis, and coagulation/serology (and changes from baseline) by cohort, treatment, and scheduled time will be provided. For Cohort 1, the baseline for treatment for DC-806 is predose on Day 1, and the baseline

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for treatment with DC-806 + Itraconazole is predose on Day 7. For Cohort 2, the baseline for treatment for DC-806 is predose on Day 1, and the baseline for treatment with DC-806 + Carbamazepine is predose on Day 18.

All laboratory data will be listed by participant, including laboratory tests not listed in the protocol. A separate listing of out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory (source data) and will be included in the listings for reference.

13.3.1 Vital Signs

Descriptive statistics summarizing vital signs (and changes from baseline) by cohort, treatment, and scheduled time will be provided. For Cohort 1, the baseline for treatment for DC-806 is predose on Day 1, and the baseline for treatment with DC-806 + Itraconazole is predose on Day 7. For Cohort 22, the baseline for treatment for DC-806 is predose on Day 1, and the baseline for treatment with DC-806 + Carbamazepine is predose on Day 18.

All vital signs will be listed by participant.

13.3.2 Electrocardiograms (ECGs)

The means of triplicate measurements for continuous parameters and the change from baseline of the mean triplicate measurements at each scheduled timepoint will be listed by participant.

Descriptive statistics summarizing mean ECG parameters (and changes from baseline) by treatment and scheduled time will be provided. Separate tables will be provided for triplicate ECG measurements and for single ECG measurements.

For triplicate ECGs, for Cohort 1 predose for DC-806 is study Day 1, and predose for DC-806 + Itraconazole is study Day 7. For Cohort 2 predose for DC-806 is study Day 1, triplicate ECGs were not performed for DC-806 + Carbamazepine on study Day 18. A shift table of overall interpretation of the triplicate ECG results at predose and +1 hours postdose per treatment will be summarized by the number and percentage of participants in each category (Normal, Abnormal - Not Clinically Significant (NCS) and Abnormal – Clinically Significant (CS)).

For single ECGs, a summary table will present mean ECG parameters at baseline (study Day -1 if non-missing, otherwise Screening visit will be used), and each postdose visit overall. A shift table will present the overall best clinical interpretation at baseline (study Day -1 if non-missing, otherwise Screening visit will be used) and the worst clinical interpretation at each post baseline visit overall.

All ECG parameters and the corresponding abnormalities will be listed by participant.

13.3.3 Other Observations Related to Safety

Physical Exams were performed but collected as a procedure and thus data is not included

14.0 References

Clinical Study Protocol. A PHASE 1, SINGLE-CENTER, OPEN-LABEL, 2-COHORT, FIXED-SEQUENCE, DRUG-DRUG INTERACTION STUDY TO ASSESS THE PHARMACOKINETICS OF DC-806 WHEN ORALLY ADMINISTERED ALONE, WHEN COADMINISTERED WITH ITRACONAZOLE, AND WHEN COADMINISTERED WITH CARBAMAZEPINE IN HEALTHY ADULT PARTICIPANTS . Version 1.0, Final, 08 June 2023.

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Appendix 1: List of End of Text Outputs

Output	Title	Analysis Set	Pre-Lock TFL
Section 14.1 – Disposition and Demographic Data			
Table 14.1.1	Summary of Participant Disposition	Enrolled Set	☒
Table 14.1.2.1	Summary of Demographics	Safety Set	☒
Table 14.1.2.2	Summary of Demographics	PK Sets	☒
Table 14.1.3.1	Summary of Study Drug Administration	Safety Set– Cohort 1 DC-806/Itraconazole	☒
Table 14.1.3.2	Summary of Study Drug Administration	Safety Set – Cohort 2 DC-806/Carbamazepine	☒
Section 14.2 – Pharmacokinetic Data			
Table 14.2.1.1	Summary of Plasma Concentrations	PK Itraconazole	☐
Table 14.2.1.2	Summary of Plasma Concentrations	PK Carbamazepine	☐
Table 14.2.2.1	Summary of Plasma Pharmacokinetic Parameters	PK Itraconazole	☐
Table 14.2.2.2	Summary of Plasma Pharmacokinetic Parameters	PK Carbamazepine	☐
Table 14.2.3.1	Statistical Analysis of the Effect of Itraconazole on DC-806	PK Itraconazole	☐
Table 14.2.3.2	Statistical Analysis of the Effect of Carbamazepine on DC-806	PK Carbamazepine	☐
Figure 14.2.4.1.1	Plot of Mean (±SD) Plasma Concentrations Versus Time on a Linear Scale	PK Itraconazole	☐
Figure 14.2.4.1.2	Plot of Mean (±SD) Plasma Concentrations Versus Time on a Linear Scale	PK Carbamazepine	☐
Figure 14.2.4.2.1	Plot of Mean (+SD) Plasma Concentrations Versus Time on a Semi-Log Scale	PK Itraconazole	☐
Figure 14.2.4.2.2	Plot of Mean (+SD) Plasma Concentrations Versus Time on a Semi-Log Scale	PK Carbamazepine	☐
Figure 14.2.5.1	Box-and-Whisker Plot of Plasma Pharmacokinetic Parameters	PK Itraconazole	☐
Figure 14.2.5.2	Box-and-Whisker Plot of Plasma Pharmacokinetic Parameters	PK Carbamazepine	☐
Figure 14.2.6.1.1	Plot of Individual Plasma Concentrations Versus Time on a Linear Scale	PK Itraconazole	☐
Figure 14.2.6.1.2	Plot of Individual Plasma Concentrations Versus Time on a Linear Scale	PK Carbamazepine	☐
Figure 14.2.6.2.1	Plot of Individual Plasma Concentrations Versus Time on a Semi-Log Scale	PK Itraconazole	☐

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Figure 14.2.6.2.2	Plot of Individual Plasma Concentrations Versus Time on a Semi-Log Scale	PK Carbamazepine	
Figure 14.2.7.1	Spaghetti Plot of Individual Plasma Concentrations Versus Time by Cohort and Treatment Group	PK Itraconazole	☐
Figure 14.2.7.2	Spaghetti Plot of Individual Plasma Concentration Versus Time by Cohort and Treatment Group	PK Carbamazepine	☐
Figure 14.2.8.1	Scatter Plot of Individual Plasma Pharmacokinetic Parameters	PK Itraconazole	☐
Figure 14.2.8.2	Scatter Plot of Individual Plasma Pharmacokinetic Parameters	PK Carbamazepine	☐
Section 14.3 – Safety Data			
Table 14.3.1	Summary of Adverse Events	Safety	☒
Table 14.3.2	Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety	☒
Table 14.3.3	Summary of Treatment-emergent Adverse Events by Relationship to Study Drug	Safety	☒
Table 14.3.4	Summary of Treatment-emergent Adverse Events by Severity	Safety	☒
Table 14.3.5	Summary of Laboratory Results	Safety	☒
Table 14.3.6	Summary of Vital Signs	Safety	☒
Table 14.3.7	Summary of 12-Lead Triplicate Electrocardiogram Results	Safety	☒
Table 14.3.8	Summary of 12-Lead Triplicate Electrocardiogram Clinical Interpretation Shifts from Baseline	Safety	☒
Table 14.3.9	Summary of 12-Lead Single Electrocardiogram Results	Safety	☒
Table 14.3.10	Summary of 12-Lead Single Electrocardiogram Clinical Interpretation Results	Safety	☒

Output	Title (Listings)	Pre-Lock TFL
Section 16.2.1 – Disposition		
Listing 16.2.1.1	Participant Disposition	☐
Listing 16.2.1.2	Eligibility Criteria	☒
Section 16.2.2 – Protocol Deviations		
Listing 16.2.2	Important Protocol Deviations	☒
Section 16.2.3 – Excluded Participants		
Listing 16.2.3	Analysis Sets	☒
Section 16.2.4 – Demographics and Baseline Characteristics		
Listing 16.2.4.1	Participant Demographics	☒

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Listing 16.2.4.2	Serology Test Values at Screening	☒
Listing 16.2.4.3	Alcohol and Drug Screen	☒
Listing 16.2.4.4	Medical History	☒
Listing 16.2.4.5	Prior and Concomitant Medications	☒
Section 16.2.5 – Compliance		
Listing 16.2.5	Study Drug Administration	☒
Section 16.2.6 – Response Data		
Listing 16.2.6.1.1	DC-806 Plasma Concentrations – Cohort 1 DC-806/Itraconazole	☐
Listing 16.2.6.1.2	DC-806 Plasma Concentrations – Cohort 2 DC-806/Carbamazepine	☐
Listing 16.2.6.2.1	Plasma Pharmacokinetic Parameters - Cohort 1 DC-806/Itraconazole	☐
Listing 16.2.6.2.2	Plasma Pharmacokinetic Parameters - Cohort 2 DC-806/Carbamazepine	☐
Listing 16.2.6.3.1	Plasma Pharmacokinetic Diagnostic Parameters - Cohort 1 DC-806/Itraconazole	☐
Listing 16.2.6.3.2	Plasma Pharmacokinetic Diagnostic Parameters - Cohort 2 DC-806/Carbamazepine	☐
Listing 16.2.6.4.1	Treatment Ratios of DC-806 Pharmacokinetic Parameters – Cohort 1 DC-806/Itraconazole	☐
Listing 16.2.6.4.2	Treatment Ratios of DC-806 Pharmacokinetic Parameters - Cohort 2 DC-806/Carbamazepine	☐
Section 16.2.7 – Adverse Events Data		
Listing 16.2.7.1	Adverse Events	☒
Listing 16.2.7.2	Adverse Events Leading To Study Drug Discontinuation	☒
Listing 16.2.7.3	Listing of Serious Adverse Events	☐
Listing 16.2.7.4	Listing of Deaths	☐
Section 16.2.8 – Laboratory Data		
Listing 16.2.8.1	Clinical Laboratory Results – Chemistry	☒
Listing 16.2.8.2	Clinical Laboratory Results – Hematology	☒
Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis	☒
Listing 16.2.8.4	Clinical Laboratory Results – Coagulation	☒
Listing 16.2.8.5	Abnormal Laboratory Results	☒
Section 16.2.9 Other Safety Data		
Listing 16.2.9	Vital Signs	☒
Listing 16.2.10	12-Lead Electrocardiogram Results	☒
Listing 16.2.11	Physical Examinations	☒
Listing 16.2.12	Columbia-Suicide Severity Rating Scale Results - (Cohort 2 DC-806/Carbamazepine Only)	☒

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Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.9.2.1	Statistical Methods Supporting Table 14.2.3.1
Appendix 16.1.9.2.2	Statistical Methods Supporting Table 14.2.3.2

Shells are provided in “DCE806103 Shells.pdf” to support the approved SAP.

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Appendix 2: Parameter Definitions

Plasma Parameter Data Name	Plasma Parameter Protocol Name	Description	Analyte	Programming Notes
Cmax	C_{max}	Maximum concentration.	DC-806 CCI	Cmax from WNL
Tmax	t_{max}	Time to maximum concentration..	DC-806 CCI	Tmax from WNL
AUCinf	AUC_{0-inf}	Area under the concentration-time curve from time 0 extrapolated to infinity.	DC-806 CCI	AUCINF_obs from WNL To be excluded from analysis/summaries if the following exclusion criteria are met: • Extrapolation, • Regression
AUClast	AUC_{0-t}	Area under the concentration-time curve time 0 to time of last quantifiable concentration.	DC-806 CCI	AUClast from WNL
T-HALF	$T_{1/2}$	Terminal elimination phase half-life	DC-806 CCI	HL_Lambda_z from WNL To be excluded from analysis/summaries if any of the following exclusion criteria are met: • Extrapolation • Regression • Lz1 • Span
CL/F	CL/F	Apparent clearance after extra-vascular dose.	DC-806 CCI	CL_F_obs from WNL To be excluded from analysis/summaries if any of the following exclusion criteria are met: • Extrapolation,

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				• Regression
Vz/F	Vz/F	Apparent volume of distribution after extra-vascular dose.	DC-806 CCI	Vz_F_obs from WNL To be excluded from analysis/summaries if any of the following exclusion criteria are met: • Extrapolation, • Regression

Diagnostic Parameter Data Name	Diagnostic Parameter Protocol Name	Description	SAS Programming Notes
AUC%Extrap		Percentage of AUCinf due to extrapolation from the last quantifiable concentration observed to infinity.	AUC_%Extrap_obs from WNL
Adj Rsq		Goodness of fit statistic for the log-linear terminal elimination phase	Rsq_adjusted from WNL
Lz	k_{el}	Terminal phase rate constant Note: In Phoenix, use Best Fit method used to determine regression.	Lambda_z from WNL
Lz_Start		Start time used in the regression for the determination of Lz.	Lambda_z_lower from WNL
Lz_End		End time used in the regression for the determination of Lz.	Lambda_z_upper from WNL
Lz_N		Number of points used in the regression for the determination of Lz.	No_points_lambda_z from WNL
Span		Number of half-lives used in the regression for the determination of Lz.	Span from WNL

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Appendix 3: Protocol Schedule of Assessments

Table 1 Schedule of Assessments – Cohort 1

Visit	Screening	Period 1					Period 2			Period 3					Follow-up/ET
Study Day	**-28 to -1**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**10 (±2) Days After the Last Dose of Itraconazole/at ET**
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	
Ambulatory	X														X
Admission		X													
Discharge														X	
Informed Consent	X														
Medical & Surgical History	X	X													
Demographics	X														
Physical Examination[a]	X													X	X
Body Weight	X	X													
Height and BMI Calculation	X	X													
Serology (HBsAg, anti-HCV, anti-HIV 1 and 2)	X														
Drug and Alcohol Screen	X	X													
Pregnancy Test (Females Only)[b]	X	X													X
FSH Test (Postmenopausal Females Only/NA for Surgically Sterile Females)	X														
Clinical Laboratory[c]	X	X	X		X					X	X			X	X
12-lead ECG[d]	X	X	X	X						X	X				X
Vital Signs[e]	X	X	X	X	X					X	X			X	X
Eligibility Check	X	X	X												
SD DC-806 CCI mg Administration				X						X					
QD Itraconazole CCI mg Administration							X	X	X	X	X	X	X		
Blood Sampling for PK of DC-806 CCI			X	X	X	X	X			X	X	X	X	X	
Blood Sampling for Pharmacogenomics[g]			X												
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Visit	Screening	Period 1					Period 2			Period 3					Follow-up/ET
Study Day	**-28 to -1**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**10 (±2) Days After the Last Dose of Itraconazole/at ET**
AE Monitoring[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; BMI=body mass index; ECG=electrocardiogram; ET=early termination; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; β-hCG=β-human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; NA=not applicable; PK=pharmacokinetic(s); SAE=serious adverse events; SD=single dose.

[a] Complete physical examinations will be conducted at screening and follow-up/ET. Symptom-driven physical examinations will be conducted at any time, including at discharge, per the Investigator's discretion. The physical examination at discharge on Day 11 is not mandatory and will only be symptom-driven, based on the Investigator's discretion.

[b] β-hCG will be tested in all female participants; in serum during screening, in urine on other days (if applicable). In cases of equivocal results of urine pregnancy tests, a serum pregnancy test is to be performed.

[c] Clinical laboratory tests (including clinical chemistry, hematology, coagulation [at screening only], and urinalysis): at screening; on Day -1 (admission); predose and 24 hours postdose for DC-806; and at follow-up/ET. Note: clinical laboratory tests time windows: predose has no window as long as it is the same date/prior to dosing; 24 hour postdose within ±60 minutes

[d] Single 12-lead ECGs will be performed (after participant has rested at least 5 minutes in the supine position) at screening, Day -1, Day 8 (predose) and at follow-up/ET. 12-lead ECGs will be performed in triplicate on Day 1 (predose and 1 hour postdose), and on Day 7 (predose, and 1 hour postdose). Note: ECG time windows: predose within 1 hour prior to reference dosing; 1 hour postdose ±5 minutes

[e] Vital signs (supine systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate): at screening; on Day -1 (admission); at Day 1 and day 7 predose and at 1, 2, 6, 12 and 24 hours postdose for DC-806; discharge (Day 11) and at follow-up/ET. Note: vital signs time windows: predose within 1 hour prior to reference dosing; 1 hour/2 hour/6 hour postdose ±5 minutes; 12 hour postdose ±10 minutes; 24 hour post dose ±60 minutes

[f] Blood sampling for PK of DC-806 [redacted] in plasma: at predose and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48 and 72 hours postdose on Day 1 and at predose and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 96 hours postdose on Day 7. Note: PK sampling time windows: predose sample: within 1 hour prior to dosing; <2 hours after study drug administration: ±5 minutes; ≥2 and <18 hours after study drug administration: ±10 minutes, and ≥18 hours and <72 hours after study drug administration: ±60 minutes; ≥72 hours after study drug administration: ±3 hours.

[g] Blood sampling for pharmacogenomics is optional for all participants. A single pharmacogenomic sample will be collected prior to dosing on Day 1.

[h] After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be collected and reported to the Sponsor. After initiation of study drug, all adverse events will be collected until the last follow-up visit. In addition, the Sponsor must be notified of any SAE the Investigator becomes aware of that has occurred after the last follow-up visit and that is believed to be related to study drug.

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Table 2 Schedule of Assessments – Cohort 2

Visit	Screening	Period 1					Period 2	Period 3								Follow-up/ET
Study Day	-28 to -1	-1	1 (Pre-dose)	1	2	3	4 to 17	18	19	20	21	22	23	24	25	6 (+2) Days After the Last Dose of Carbamazepine /at ET
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ambulatory	X															X
Admission		X														
Discharge															X	
Informed Consent	X															
Medical & Surgical History	X	X														
Demographics	X															
Physical Examination[a]	X														X	X
Body Weight	X	X														
Height and BMI Calculation	X	X														
Serology (HBsAg, anti-HCV, anti-HIV 1 and 2)	X															
C-SSRS	X															
Drug and Alcohol Screen	X	X														
Pregnancy Test (Females Only)[b]	X	X														X
FSH Test (Postmenopausal Females Only/NA for Surgically Sterile Females)	X															
Clinical Laboratory[c]	X	X	X		X			X	X						X	X
12-lead ECG[d]	X	X	X	X				X	X							X
Vital Signs[e]	X	X	X	X	X			X	X						X	X
Eligibility Check	X	X	X													
SD DC-806 CCI mg Administration				X				X								
BID carbamazepine Administration							X	X	X	X	X	X	X	X		
Blood Sampling for PK of DC-806 CCI [redacted]			X	X	X	X	X[f]	X	X	X	X	X				
Blood sampling for pharmacogenomics[g]			X													
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
AE Monitoring[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

AE=adverse event; BID=twice daily; BMI=body mass index; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; β-hCG=β-human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; NA=not applicable; PK=pharmacokinetic(s); SAE=serious adverse events; SD=single dose.

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[a] Complete physical examinations will be conducted at screening and follow-up/ET. Symptom-driven physical examinations will be conducted at any time, including at discharge, per the Investigator's discretion. The physical examination at discharge on Day 25 is not mandatory and will only be symptom-driven, based on the Investigator's discretion.
[b] β-hCG will be tested in all female participants; in serum during screening, in urine on other days (if applicable). In cases of equivocal results of urine pregnancy tests, a serum pregnancy test is to be performed.
[c] Clinical laboratory tests (including clinical chemistry, hematology, coagulation [at screening only], and urinalysis): at screening; on Day -1 (admission); predose and 24 hours postdose for DC-806; and at follow-up/ET. Note: clinical laboratory tests time windows: predose has no window as long as it is the same date/prior to dosing; 24 hour postdose within ±60 minutes
[d] Single 12-lead ECGs will be performed (after participant has rested at least 5 minutes in the supine position) at screening, Day -1, Day 18 (predose), Day 19 (predose) and at follow-up/ET. 12-lead ECGs will be performed in triplicate on Day 1 (predose and 1 hour postdose). Note: ECG time windows: predose within 1 hour prior to reference dosing; 1 hour postdose ±5 minutes
[e] Vital signs (supine systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate): at screening; on Day -1 (admission); at predose and at 1, 2, 6, and 24 hours postdose for DC-806; discharge (Day 25) and at follow-up/ET. Note: vital signs time windows: predose within 1 hour prior to reference dosing; 1 hour/2 hour/6 hour postdose ±5 minutes; 12 hour postdose +10 minutes; 24 hour post dose ±60 minutes
[f] Blood sampling for PK of DC-806 CCI in plasma: at predose and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours postdose on Day 1 and at predose and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, 72, and 96 hours postdose on Day 18. Note: PK sampling time windows: predose sample: within 1 hour prior to dosing; <2 hours after study drug administration: ±5 minutes; ≥2 and <18 hours after study drug administration: ±10 minutes, and ≥18 hours and <72 hours after study drug administration: ±60 minutes; ≥72 hours after study drug administration: ±3 hours.
[g] Whole blood sampling for pharmacogenomics is optional for all participants. A single pharmacogenomic sample will be collected prior to dosing on Day 1.
[h] After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be collected and reported to the Sponsor. After initiation of study drug, all adverse events will be collected until the last follow-up visit/ET. In addition, the Sponsor must be notified of any SAE the Investigator becomes aware of that has occurred after the last follow-up visit and that is believed to be related to study drug.

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Appendix 4: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ADaM	Analysis data model
ANOVA	Analysis of variance
BMI	Body mass index
BQL	Below the quantifiable limit
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CSR	Clinical study report
CS	Clinically significant
CRF	Case report form
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
GMR	Geometric mean ratio
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LLOQ	Lower limit of quantification
LS	Least squares
LSGM	Least squares geometric mean
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
PD	Pharmacodynamic
PK	Pharmacokinetic
QA'd	Quality assured
QC'd	Quality controlled
SAP	Statistical analysis plan
SAE	Serious adverse event
SD	Standard deviation
SDTM	Study data tabulation model
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
WI	Work Instruction
WNL	WinNonlin

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15.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes
07-Aug-2023	PPD	Draft Version 1
30-Aug-2023		Draft Version 2
27-Sep-2023		Draft Version 3 revised as per DICE comments and ICON PK
13-Oct-2023		Final SAP and shells

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Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Code=AUCIFO

Model Information

Data Set	WORK.PARM30
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
TRTPN	21	3
SUBJID	CCI	[redacted]

Dimensions

Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	32

Number of Observations

Number of Observations Read	32
Number of Observations Used	32
Number of Observations Not Used	0

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Code=AUCIFO

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	45.16811039	
1	3	33.40804671	0.02188010
2	1	33.13082327	0.00209906
3	1	33.10617835	0.00002515
4	1	33.10589901	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr > Z
SUBJID	0.1581	0.06656	2.37	0.0088
Residual	0.05501	0.02051	2.68	0.0037

Fit Statistics

-2 Res Log Likelihood	33.1
AIC (Smaller is Better)	37.1
AICC (Smaller is Better)	37.6
BIC (Smaller is Better)	38.8

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Code=AUCIFO

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTPN	1	14.8	506.95	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT1 vs TRT3	1.9195	0.08525	14.8	22.52	<.0001	0.1	1.7699	2.0691

Least Squares Means

Effect	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	1	6.9112	0.1120	20.4	61.73	<.0001	0.1	6.7183	7.1042
TRTPN	3	8.8307	0.1155	22	76.49	<.0001	0.1	8.6325	9.0290

Differences of Least Squares Means

Effect	Planned Treatment (N)	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	1	3	-1.9195	0.08525	14.8	-22.52	<.0001	0.1	-2.0691	-1.7699

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Code=AUCLST

Model Information	
Data Set	WORK.PARM30
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
TRTPN	2	1 3
SUBJID	CCI	

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	33

Number of Observations	
Number of Observations Read	33
Number of Observations Used	33
Number of Observations Not Used	0

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Code=AUCLST

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	48.06701718	
1	3	35.84209158	0.00059029
2	1	35.83562425	0.00000198
3	1	35.83560324	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr > Z
SUBJID	0.1672	0.07055	2.37	0.0089
Residual	0.05963	0.02162	2.76	0.0029

Fit Statistics

-2 Res Log Likelihood	35.8
AIC (Smaller is Better)	39.8
AICC (Smaller is Better)	40.3
BIC (Smaller is Better)	41.5

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Code=AUCLST

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTPN	1	15.4	487.64	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT1 vs TRT3	1.9019	0.08613	15.4	22.08	<.0001	0.1	1.7512	2.0526

Least Squares Means

Effect	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	1	6.8909	0.1155	20.6	59.65	<.0001	0.1	6.6919	7.0899
TRTPN	3	8.7928	0.1173	21.4	74.99	<.0001	0.1	8.5912	8.9944

Differences of Least Squares Means

Effect	Planned Treatment (N)	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	1	3	-1.9019	0.08613	15.4	-22.08	<.0001	0.1	-2.0526	-1.7512

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Code=CMAX

Model Information

Data Set	WORK.PARM30
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
TRTPN	2	1 3
SUBJID	CCI	

Dimensions

Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	33

Number of Observations

Number of Observations Read	33
Number of Observations Used	33
Number of Observations Not Used	0

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Code=CMAX

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	57.88037243	
1	3	55.29862599	0.00013325
2	1	55.29851377	0.00000001

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr > Z
SUBJID	0.1217	0.08433	1.44	0.0745
Residual	0.1929	0.06925	2.79	0.0027

Fit Statistics

-2 Res Log Likelihood	55.3
AIC (Smaller is Better)	59.3
AICC (Smaller is Better)	59.7
BIC (Smaller is Better)	61.0

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Code=CMAX

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTPN	1	15.9	77.41	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT1 vs TRT3	1.3568	0.1542	15.9	8.80	<.0001	0.1	1.0875	1.6261

Least Squares Means

Effect	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	1	5.9476	0.1360	27.3	43.72	<.0001	0.1	5.7160	6.1793
TRTPN	3	7.3045	0.1400	27.9	52.18	<.0001	0.1	7.0663	7.5426

Differences of Least Squares Means

Effect	Planned Treatment (N)	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	1	3	-1.3568	0.1542	15.9	-8.80	<.0001	0.1	-1.6261	-1.0875

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Code=AUCIFO

Model Information	
Data Set	WORK.PARM30
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
TRTPN	2	4 6
SUBJID	[redacted]	[redacted]

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	[redacted]
Subjects	1
Max Obs per Subject	29

Number of Observations	
Number of Observations Read	29
Number of Observations Used	29
Number of Observations Not Used	0

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Code=AUCIFO

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	10.02430568	
1	3	7.35102792	0.00017238
2	1	7.34727414	0.00000038
3	1	7.34726601	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr > Z
SUBJID	0.02921	0.01995	1.46	0.0716
Residual	0.03966	0.01559	2.54	0.0055

Fit Statistics

-2 Res Log Likelihood	7.3
AIC (Smaller is Better)	11.3
AICC (Smaller is Better)	11.8
BIC (Smaller is Better)	12.9

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Code=AUCIFO

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTPN	1	14.1	180.90	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT4 vs TRT6	-1.0266	0.07633	14.1	-13.45	<.0001	0.1	-1.1610	-0.8922

Least Squares Means

Effect	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	4	8.9857	0.06759	24.3	132.95	<.0001	0.1	8.8701	9.1013
TRTPN	6	7.9591	0.06979	24.9	114.05	<.0001	0.1	7.8399	8.0783

Differences of Least Squares Means

Effect	Planned Treatment (N)	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	4	6	1.0266	0.07633	14.1	13.45	<.0001	0.1	0.8922	1.1610

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Code=AUCLST

Model Information	
Data Set	WORK.PARM30
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
TRTPN	2	4 6
SUBJID	[redacted]	[redacted]

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	[redacted]
Subjects	1
Max Obs per Subject	30

Number of Observations	
Number of Observations Read	30
Number of Observations Used	30
Number of Observations Not Used	0

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Code=AUCLST

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	12.26070153	
1	3	9.82963650	0.00000482
2	1	9.82953572	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr > Z
SUBJID	0.02994	0.02132	1.40	0.0801
Residual	0.04447	0.01710	2.60	0.0046

Fit Statistics

-2 Res Log Likelihood	9.8
AIC (Smaller is Better)	13.8
AICC (Smaller is Better)	14.3
BIC (Smaller is Better)	15.4

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTPN	1	14.3	162.16	<.0001

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Code=AUCLST

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT4 vs TRT6	-1.0013	0.07863	14.3	-12.73	<.0001	0.1	-1.1396	-0.8630

Least Squares Means

Effect	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	4	8.9521	0.06820	24.5	131.27	<.0001	0.1	8.8355	9.0686
TRTPN	6	7.9507	0.07263	25.8	109.47	<.0001	0.1	7.8268	8.0746

Differences of Least Squares Means

Effect	Planned Treatment (N)	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	4	6	1.0013	0.07863	14.3	12.73	<.0001	0.1	0.8630	1.1396

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Code=CMAX

Model Information	
Data Set	WORK.PARM30
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
TRTPN	2	4 6
SUBJID	[redacted]	[redacted]

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	[redacted]
Subjects	1
Max Obs per Subject	30

Number of Observations	
Number of Observations Read	30
Number of Observations Used	30
Number of Observations Not Used	0

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Code=CMAX

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	37.29816668	
1	3	32.73262692	0.00145686
2	1	32.71823993	0.00001120
3	1	32.71813443	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr > Z
SUBJID	0.09359	0.05258	1.78	0.0375
Residual	0.08621	0.03288	2.62	0.0044

Fit Statistics

-2 Res Log Likelihood	32.7
AIC (Smaller is Better)	36.7
AICC (Smaller is Better)	37.2
BIC (Smaller is Better)	38.3

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Code=CMAX

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTPN	1	14.4	68.66	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT4 vs TRT6	-0.9101	0.1098	14.4	-8.29	<.0001	0.1	-1.1032	-0.7171

Least Squares Means

Effect	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	4	7.9168	0.1060	22.9	74.68	<.0001	0.1	7.7351	8.0986
TRTPN	6	7.0067	0.1119	24.5	62.61	<.0001	0.1	6.8154	7.1980

Differences of Least Squares Means

Effect	Planned Treatment (N)	Planned Treatment (N)	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	4	6	0.9101	0.1098	14.4	8.29	<.0001	0.1	0.7171	1.1032