

Stistical Analysis Plan J5B-MC-FHAE V1

A Phase 1, Single-Center, Open-Label, Fixed-Sequence Study to Evaluate the Effect of DC-806 on the Single Dose Pharmacokinetics of CYP450 Enzyme and Transporter Substrates in Healthy Participants

NCT06092931

Approval Date: 08-Nov-2023

Statistical Analysis Plan

Sponsor:	DICE Therapeutics, Inc. A wholly owned subsidiary of Eli Lilly and Company
Protocol Number:	DCE806104
Protocol Title:	A PHASE 1, SINGLE-CENTER, OPEN-LABEL, FIXED-SEQUENCE STUDY TO EVALUATE THE EFFECT OF DC-806 ON THE SINGLE DOSE PHARMACOKINETICS OF CYP450 ENZYME AND TRANSPORTER SUBSTRATES IN HEALTHY PARTICIPANTS
ICON Project Identifier:	DITBEE43-0D1NX8
SAP Version Date:	08-Nov-2023

1.0 Approvals

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

Name of Biostatistician / Title:	PPD / Biostatistician, ICON	PPD 09 Nov 2023 15:30:22 UTC (Z) REASON: I approve this document 05bb4a9a-85b6-4839-b09f-94b4bfc5275
Signature of Biostatistician / Date:		
Name of Sponsor Representative / Title:	PPD / Director of Biostatistics, DICE Therapeutics, Inc.	PPD 09 Nov 2023 15:46:38 UTC (Z) REASON: I approve this document e601950e-329c-40ed-8656-1911b52a9c4e
Signature of Sponsor Representative / Date:		

2.0 Table of Contents

1.0 Approvals	1
2.0 Table of Contents.....	2
3.0 Introduction	4
4.0 Changes to Analysis.....	4
4.1 Changes from Protocol.....	4
4.2 Changes from Previous Version of Approved SAP	4
5.0 Study Objectives	4
5.1 Primary.....	4
5.1.1 Primary Endpoints	4
5.2 Secondary	4
5.2.1 Secondary Endpoints.....	5
5.3 Exploratory.....	5
5.3.1 Exploratory Endpoints	5
6.0 Study Design.....	5
6.1 Sample Size Considerations.....	7
6.2 Randomization and Blinding.....	7
7.0 Overview of Planned TFL Deliveries.....	8
7.1 Pre-lock TFL	8
7.2 Final Analysis.....	8
8.0 Definitions and General Analysis Methods.....	8
8.1 General Data Handling	8
8.1.1 Rounding	8
8.1.2 Imputation.....	9
8.1.3 Daylight Savings Time Adjustments	9
8.1.4 General Descriptive Statistics.....	9
8.1.5 Pooling.....	9
8.1.6 Unscheduled Measurements.....	9
8.2 Common Variable Definitions	10
8.2.1 Baseline Definition	10
8.2.2 Treatment/Participant Grouping.....	10
8.2.3 ADaM Datasets and Metadata.....	10
8.3 Software	10
8.4 Statistical Methods.....	10
8.4.1 Statistical Outlier Determination	10
8.4.2 Hypothesis Testing.....	11
8.5 TFL Layout	11

9.0 Analysis Sets.....	11
9.1 Enrolled Set.....	11
9.2 Safety Set.....	11
9.3 Pharmacokinetic Set	11
10.0 Demographic Data.....	11
10.1 Participant Disposition.....	11
10.2 Protocol Deviations.....	11
10.3 Demographics	12
10.4 Medical History.....	12
10.5 Participant Characteristics	12
10.6 Prior and Concomitant Medications	12
10.7 Treatment Compliance and Exposure.....	12
11.0 Pharmacokinetic Data	12
11.1 Pharmacokinetic Variables.....	12
11.2 Plasma Pharmacokinetic Summaries.....	12
11.2.1 Plasma Concentrations	12
11.2.2 Plasma Pharmacokinetic Parameters.....	13
12.0 Safety Data.....	14
12.1 Adverse Events (AEs).....	14
12.2 Deaths and Serious Adverse Events (SAEs).....	15
12.3 Laboratory Data	15
12.4 Vital Signs.....	15
12.5 Electrocardiograms (ECGs)	15
12.6 Other Observations Related to Safety	16
13.0 References	16
Appendix 1: List of End of Text Outputs	17
Appendix 2: Parameter Definitions.....	22
Appendix 3: Protocol Schedule of Assessments	25
Appendix 4: Glossary of Abbreviations	32
14.0 Document History	33

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 DCE806104.

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 27-Sep-2023 (including all amendments up to this protocol date) and the eCRFs dated 13-Oct-2023 Version 1.0.

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 DC-806 on the PK of CYP3A4 substrate midazolam and its active metabolite, 1-hydroxymidazolam, CYP2C8 substrate repaglinide, P-gp transporter substrate digoxin and BCRP/OATP1B1 transporter substrate rosuvastatin in healthy participants.

5.1.1 Primary Endpoints

Plasma PK parameters of midazolam, 1-hydroxymidazolam, repaglinide, digoxin and rosuvastatin in the absence and presence of steady state DC-806: C_{max} , AUC_{0-t} , AUC_{0-inf} .

5.2 Secondary

To evaluate the safety and tolerability of administering DC-806 alone and in the presence of CYP3A4 substrate midazolam, CYP2C8 substrate repaglinide, P-gp transporter substrate digoxin and BCRP/OATP1B1 transporter substrate rosuvastatin in healthy participants.

5.2.1 Secondary Endpoints

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

5.3 Exploratory

CCI

5.3.1 Exploratory Endpoints

- CCI

6.0 Study Design

This is a phase 1, single-center, open-label, fixed-sequence, 2-cohort study in up to 28 healthy male and female participants (up to CCI participants per cohort). This study will evaluate the effect of DC-806 (CCI mg BID) on the PK of CYP3A4 probe substrate midazolam and its active metabolite, 1--hydroxymidazolam, CYP2C8 substrate repaglinide, P-gp transporter substrate digoxin and BCRP/OATP1B1 transporter substrate rosuvastatin in healthy participants.

This study will consist of 2 cohorts with DC-806 serving as the perpetrator drug in each cohort.

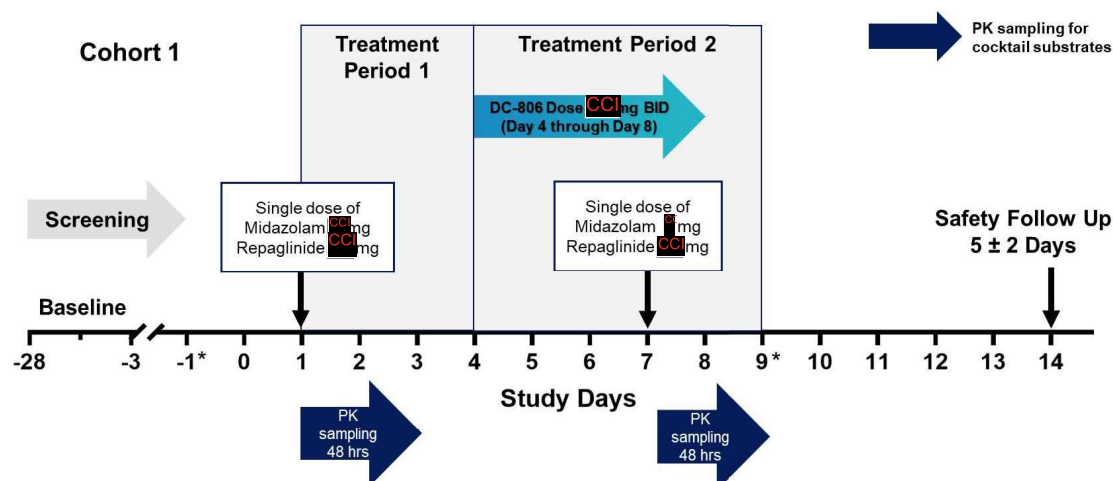
Cohort 1 Study Treatment; midazolam (CYP3A4 substrate), repaglinide (CYP2C8 substrate):

Each participant will receive a single oral dose of the 2-probe substrate cocktail (CCI mg midazolam and CCI mg repaglinide) under fasted conditions in the morning on Day 1 of Period 1. In Period 2, participants will receive twice-daily oral doses of CCI mg DC-806 on Days 4 through 8. A single oral dose of the 2--probe substrate cocktail (CCI mg midazolam and CCI mg repaglinide) will be administered under fasted conditions 1.5 hours ($\pm$ 15 min) after DC-806 dosing in the morning of Day 7 while DC-806 BID dosing will be continued until the end of Day 8 (final dose given in the evening of Day 8).

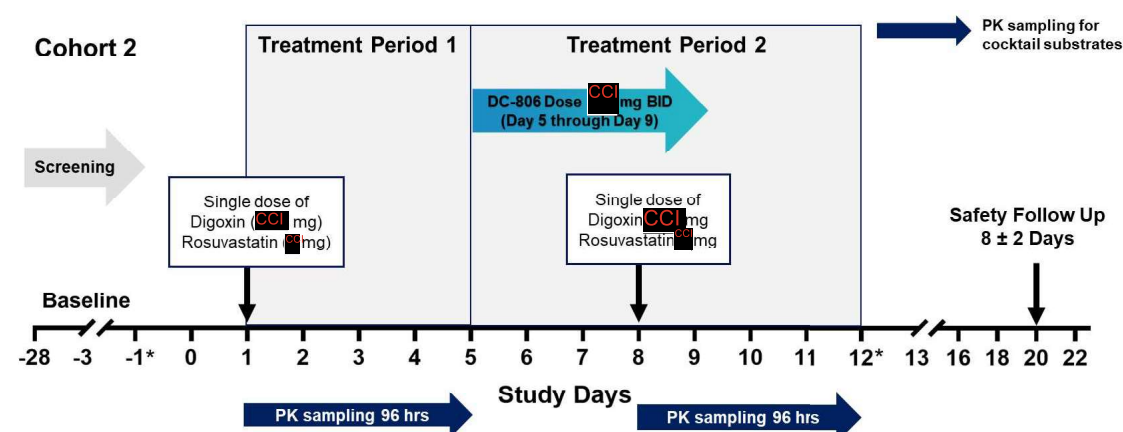
Cohort 2 Study Treatment; digoxin, (P-gp substrate), rosuvastatin (BCRP/OATP1B1 substrate):

Each participant will receive a single oral dose of the 2-probe substrate cocktail (CCI mg digoxin and CCI mg rosuvastatin) under fasted conditions in the morning on Day 1 of Period 1. In Period 2, participants will receive CCI mg of DC-806 (BID) on Days 5 through 9. A single oral dose of the 2-probe substrate cocktail (CCI mg digoxin and CCI mg rosuvastatin) will be administered under fasted conditions in the morning of Day 8, 1.5 hour ($\pm$ 15 min) after DC-806 dosing while DC-806 BID dosing will be continued until the end of Day 9 (final dose given in the evening of Day 9).

A diagram of the study design is presented in [Figure 1](#) (Cohort 1) and [Figure 2](#) (Cohort 2) shown below.

Figure 1 Study Design Schematic – Cohort 1

*Participants admitted to the clinical site on Day -1 and discharged on Day 9 after completion of assessments.
 Safety follow-up/ET: 5 (±2) days after collection of the last PK blood sample on Day 9 or at the time of ET.
 BID=twice daily; ET=early termination; PK=pharmacokinetic(s)

Figure 2 Study Design Schematic – Cohort 2

*Participants admitted to the clinical site on Day -1 and discharged on Day 12 after completion of assessments.
 Safety follow-up/ET: 8 (±2) days after collection of the last PK blood sample on Day 12 or at the time of ET.
 BID=twice daily; ET=early termination; PK=pharmacokinetic(s)

Study Schedule

Screening : Between Day -28 and Day -1 (admission).

Treatment period : Participants in Cohort 1 and Cohort 2 will be confined in the clinic for 2 treatment periods.

Cohort 1 (midazolam [CYP3A4 substrate], repaglinide [CYP2C8 substrate]):

Treatment Period 1: 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.

Treatment Period 2: Participants will be dosed with DC-806 on Day 4 in the morning (at the end of Period 1), the day of the first drug administration in Period 2. Participants will be discharged on Day 9 after completion of the assessments.

Cohort 2 (digoxin [P-gp substrate], rosuvastatin [BCRP/OATP1B1 substrate])

Treatment Period 1: 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.

Treatment Period 2: Participants will be dosed with DC-806 on Day 5 in the morning (after the collection of last PK sample (96 hours) at the end of Period 1), the day of the first drug administration in Period 2. Participants will be discharged on Day 12 after completion of the assessments.

Follow-up/ET : 5 ($\pm$ 2) days after collection of the last PK blood sample on Day 9 (Cohort 1), 8 ($\pm$ 2) days after collection of the last PK blood sample on Day 12 (Cohort 2), or at ET.

6.1 Sample Size Considerations

A total of approximately 28 healthy male and female participants will be enrolled in the study with up to **CC** to be enrolled in each cohort, aiming to have approximately **CC** evaluable participants per cohort assuming a **CC**% 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 28 participants (**CC** per cohort) has been selected to provide adequate information on effect of DC-806 on the PK of CYP3A4 substrate midazolam and its active metabolite 1-hydroxymidazolam, CYP2C8 substrate repaglinide, P-gp transporter substrate digoxin and BCRP/OATP1B1 transporter substrate rosuvastatin in healthy participants.

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 safety TFL produced after database freeze and prior to lock. This draft of the safety tables, figures, and listings (TFLs) 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 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.

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 place	+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} , C _{max,ss} , C _{trough,ss} 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 _{max,ss} , 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

On November 5, 2023 at 2:00 am the clocks change to 1:00 am as Daylight Savings Time ends. All clinic procedures for the remainder of the treatment period will be moved back by one hour after daylight savings time ends. All duration (i.e., AE duration, relative time from dosing for PK) calculations for times post-daylight savings time adjustment that will be relative to a time prior to daylight savings will need to be programmatically adjusted for the hour that was gained on the morning of November 5.

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. For any deviations from the general set of descriptive statistics they 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 (unless explicitly specified otherwise).

8.2 Common Variable Definitions

8.2.1 Baseline Definition

Unless stated otherwise, baseline is defined as the last observation recorded before the first study drug administration in Period 1 of each cohort. The last observation can be an unscheduled/repeated measurement.

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, midazolam, repaglinide, digoxin, rosuvastatin
Treatments	<u>Cohort 1 DC-806/ Midazolam + Repaglinide</u> - Midazolam + Repaglinide - DC-806 - DC-806 + Midazolam and Repaglinide <u>Cohort 2 DC-806/ Digoxin + Rosuvastatin</u> - Digoxin + Rosuvastatin - DC-806 - DC-806 + Digoxin and Rosuvastatin
Dose Level	<u>Cohort 1 DC-806/ Midazolam + Repaglinide</u> ■ mg midazolam and ■■ mg repaglinide QD Day 1 ■■■ mg DC-806 Alone BID Days 4-6 ■■■ mg DC-806 BID + ■ mg midazolam and ■■ mg repaglinide QD Day 7 <u>Cohort 2 DC-806/ Digoxin + Rosuvastatin</u> ■■■ mg digoxin and ■ mg rosuvastatin QD Day 1 ■■■ mg DC-806 Alone BID Days 5-7 ■■■ mg DC-806 BID + ■■ mg digoxin and ■ mg rosuvastatin QD Day 8

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 2.1 and Implementation Guide (ADaMIG) Version 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. Slight 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 participant level Analysis Sets (populations) will be used for summaries in the study.

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 all participants who have received any amount of DC-806, midazolam, repaglinide, digoxin or rosuvastatin. This set will be used for the safety data summaries, baseline characteristic summaries, and PK concentration summaries. This set will be analyzed as treated. When summaries are generated by cohort, the overall Safety Set will be split into the following subsets:

- Safety Set – Cohort 1 DC-806/Midazolam + Repaglinide
- Safety Set – Cohort 2 DC-806/Digoxin + Rosuvastatin

9.3 Pharmacokinetic Set

The PK Set will consist of all participants who have received at least 1 dose of DC-806, midazolam, repaglinide, digoxin or rosuvastatin and provided sufficient bioanalytical assessment results to calculate reliable PK parameter estimates. This set will be used for the PK parameter summaries and primary analysis. This set will be analyzed as treated. When summaries are generated by cohort, the overall PK Set will be split into the following subsets:

- PK Set – Cohort 1 DC-806/Midazolam + Repaglinide
- PK Set – Cohort 2 DC-806/Digoxin + Rosuvastatin

10.0 Demographic Data

10.1 Participant Disposition

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

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/m²). 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 clinical laboratory measurements including serology (HBsAg, anti-HCV, and anti-HIV 1 and 2), drug screen and pregnancy test and, if collected, COVID test results, will be listed. Results from the Columbia-Suicide Severity Rating Scale at screening for Cohort 1 will also 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 (version 2023MAR01 GLOBAL B3). All prior and 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 dose of study drug, the medication will not be flagged as prior.

10.7 Treatment Compliance and Exposure

The number of participants receiving each dose of study drug per visit day and timepoint (AM, PM) will be summarized by cohort.

11.0 Pharmacokinetic Data

11.1 Pharmacokinetic Variables

Concentrations of midazolam and its active metabolite (1-hydroxymidazolam), repaglinide, digoxin, rosuvastatin, and DC-806 will be collected in plasma.

PK parameters of midazolam and its active metabolite (1-hydroxymidazolam), repaglinide, digoxin, rosuvastatin, and DC-806 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 midazolam and its active metabolite (1-hydroxymidazolam), repaglinide, digoxin, rosuvastatin, and DC-806 below the quantifiable limit (BQL) will be set to 0 in the computation of descriptive statistics. Descriptive statistics (number of participants, mean, SD, coefficient of variation [%CV], median, min, max, geometric mean, 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 for probe substrates and DC-806.

Linear (+/-SD) and semi-logarithmic (+SD) plots of the arithmetic mean plasma concentration by scheduled sampling time will be provided for each substrate (and relevant metabolite) by cohort and treatment (treatments with and without DC-806 on each plot). These plots will show time in hours. The plots will

present all calculated means and linear plots will include a reference line for the lower limit of quantification (LLOQ).

Linear (+/-SD) and semi-logarithmic (+SD) plots of the arithmetic mean trough (predose) plasma concentrations versus time will be provided for DC-806 to visually assess the achievement of steady state. Linear plots will include a reference line for the lower limit of quantification (LLOQ).

Linear and semi-logarithmic plots of the individual plasma concentrations by actual sampling time will be provided by participant (one participant per page, overlaying both treatments for probe substrates figures). These plots will show time in hours. Individual plots will use the BQL handling procedure described below for "Plasma Pharmacokinetic Parameters". 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 midazolam and its active metabolite (1-hydroxymidazolam), repaglinide, digoxin, rosuvastatin, and DC-806 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, SD, %CV, median, min, max, and geometric mean) will be used to summarize the calculated PK parameters by cohort and treatment. For t_{max} and $t_{max,ss}$, only median, min and max will be presented.

Scatter plots 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, with both treatments presented per plot.

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 each substrate (and relevant metabolite), and with both treatments presented per plot.

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-inf} , CL/F, Vz/F
Regression	Adj Rsq < 0.8	AUC_{0-inf} , $t_{1/2}$, CL/F, Vz/F
Span	Span <= 2	AUC_{0-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, parameters that meet the exclusion criteria will be accompanied by an indication of criteria met.

Diagnostic parameters are listed but not summarized.

11.2.2.2 Statistical Analysis of PK parameters

The effect of DC-806 on the PK of each probe substrate will be assessed using the geometric least-squares (LS) mean ratio (GMR) and 90% confidence intervals of GMR of the primary plasma PK parameters: C_{max} , AUC_{0-t} and AUC_{0-inf} for each substrate (and relevant metabolite). 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 each probe substrate. 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, for each substrate (and relevant metabolite) probe cocktail substrate treatments administered alone (either midazolam and repaglinide, or digoxin and rosuvastatin) 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 concomitant 90% confidence interval.

12.0 Safety Data

12.1 Adverse Events (AEs)

Treatment-emergent adverse events (TEAE) 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 the probe substrate cocktail of midazolam and repaglinide. TEAEs occurring following dosing on Day 4 but before dosing on Day 7 will be counted under treatment with DC-806 alone. TEAEs occurring following dosing on Day 7 will be counted under treatment with DC-806 coadministered with the probe substrate cocktail of midazolam and repaglinide. Cohort 1 AE summary tables will be presented by treatment (Midazolam + Repaglinide, DC-806, DC-806 + Midazolam + Repaglinide) and overall.

For Cohort 2, TEAEs occurring following dosing on Day 1 but before dosing on Day 5 will be counted under treatment with the probe substrate cocktail of digoxin and rosuvastatin. TEAEs occurring following dosing on Day 5 but before dosing on Day 9 will be counted under treatment with DC-806 alone. TEAEs occurring following dosing on Day 8 will be counted under treatment with DC-806 coadministered with the probe substrate of digoxin and rosuvastatin. Cohort 2 AE summary tables will be presented by treatment (Digoxin + Rosuvastatin, DC-806, DC-806 + Digoxin + Rosuvastatin) and overall.

Note that for AE summary tables that count the number and percentage of subjects with an AE, a given participant may be counted under more than one treatment period ([Midazolam + Repaglinide, DC-806, and DC-806 + Midazolam + Repaglinide] or [Digoxin + Rosuvastatin, DC-806, and DC-806 + Digoxin + Rosuvastatin]). However, the overall column is counted on a per participant basis, also selecting each participant's most drug-related and most severe event where specified. Thus counts in the overall column may not be a simple sum of participant counts across the three treatment periods.

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 by treatment and overall.

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, for each treatment and overall.

A summary of the number and percentage of participants reporting each TEAE and number of TEAEs will be presented by relationship to study drug (UNLIKELY RELATED and NOT 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, for each treatment and overall.

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, for each treatment and overall.

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

Separate listings of AEs leading to study drug discontinuation and study discontinuation will be provided.

12.2 Deaths and Serious Adverse Events (SAEs)

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

12.3 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 (and changes from baseline) by cohort, visit, and scheduled time will be provided. For Cohort 1, the baseline is predose on Day 1. For Cohort 2, the baseline is predose on Day 1.

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.

12.4 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 is predose on Day 1. For Cohort 2, the baseline is predose on Day 1.

All vital signs will be listed by participant.

12.5 Electrocardiograms (ECGs)

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, the average of triplicate ECG will be computed per participant and visit. For Cohort 1, a summary table of descriptive statistics for averaged ECG values and changes from baseline study Day 1 (predose) to study Day 6 (predose and +2 hours postdose) will be presented. For Cohort 2 averaged ECG values and changes from baseline study Day 1 (predose) to Study Day 7 (predose and +2 hours postdose)

will be presented. A shift table of overall clinical interpretation of the triplicate ECG results from baseline study Day 1 (predose) to study Day 6/7 (predose and +2 hours postdose) will be summarized by the number and percentage of participants in each category (Normal, Abnormal - Not Clinically Significant (NCS) and Abnormal – Clinically Significant (CS)). The shift table will present the overall best clinical interpretation from the set of triplicate ECGs at baseline and the worst clinical interpretation from the set of triplicate ECGs at each subsequent post baseline visit overall.

For single ECGs, summary table of descriptive statistics will include study Day 7 (predose and +2 hours postdose) and the followup/early termination visit for Cohort 1. For Cohort 2, study Day 8 (predose and +2 hours and +6 hours postdose), study Day 9 (predose), and followup/early termination visit will be presented. A shift table of clinical interpretation results from Day 7 (cohort 1)/Day 8 (cohort 2) predose to subsequent visits/timepoints will also be presented.

All ECG parameters and the corresponding abnormalities will be listed by participant. An additional listing will be provided for the averaged triplicate ECGs.

12.6 Other Observations Related to Safety

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

13.0 References

Clinical Study Protocol. A PHASE 1, SINGLE-CENTER, OPEN-LABEL, FIXED-SEQUENCE STUDY TO EVALUATE THE EFFECT OF DC-806 ON THE SINGLE DOSE PHARMACOKINETICS OF CYP450 ENZYME AND TRANSPORTER SUBSTRATES IN HEALTHY PARTICIPANTS. Version 2.0, Final, 27 September 2023.

Appendix 1: List of End of Text Outputs

Output	Title	Analysis Set	Pre-Lock TFL
<i>Section 14.1 – Disposition and Demographic Data</i>			
Table 14.1.1	Summary of Participant Disposition	Enrolled	☒
Table 14.1.2.1	Summary of Demographics	Safety	☒
Table 14.1.2.2	Summary of Demographics	PK	☒
Table 14.1.3.1	Summary of Study Drug Administration	Cohort 1 Safety	☒
Table 14.1.3.2	Summary of Study Drug Administration	Cohort 2 Safety	☒
<i>Section 14.2 – Pharmacokinetic Data</i>			
Table 14.2.1.1	Summary of Midazolam, 1-hydroxymidazolam, and Repaglinide Plasma Concentrations	Cohort 1 PK	☐
Table 14.2.1.2	Summary of DC-806 Plasma Concentrations	Cohort 1 PK	☐
Table 14.2.1.3	Summary of Digoxin and Rosuvastatin Plasma Concentrations	Cohort 2 PK	☐
Table 14.2.1.4	Summary of DC-806 Plasma Concentrations	Cohort 2 PK	☐
Table 14.2.2.1	Summary of Midazolam, 1-hydroxymidazolam, and Repaglinide Plasma Pharmacokinetic Parameters	Cohort 1 PK	☐
Table 14.2.2.2	Summary of DC-806 Plasma Pharmacokinetic Parameters	Cohort 1 PK	☐
Table 14.2.2.3	Summary of Digoxin and Rosuvastatin Plasma Pharmacokinetic Parameters	Cohort 2 PK	☐
Table 14.2.2.4	Summary of DC-806 Plasma Pharmacokinetic Parameters	Cohort 2 PK	☐
Table 14.2.3.1	Statistical Analysis of the Effect of DC-806 on Midazolam and Repaglinide	Cohort 1 PK	☐
Table 14.2.3.2	Statistical Analysis of the Effect of DC-806 on Digoxin and Rosuvastatin	Cohort 2 PK	☐
Figure 14.2.4.1.1	Mean ($\pm$ SD) Midazolam, 1-hydroxymidazolam, and Repaglinide Plasma Concentrations Versus Time on a Linear Scale	Cohort 1 PK	☐
Figure 14.2.4.1.2	Mean (+SD) Midazolam, 1-hydroxymidazolam, and Repaglinide Plasma Concentrations Versus Time on a Semi-Log Scale	Cohort 1 PK	☐
Figure 14.2.4.2.1	Mean ($\pm$ SD) Digoxin and Rosuvastatin Plasma Concentrations Versus Time on a Linear Scale	Cohort 2 PK	☐
Figure 14.2.4.2.2	Mean (+SD) Digoxin and Rosuvastatin Plasma Concentrations Versus Time on a Semi-Log Scale	Cohort 2 PK	☐
Figure 14.2.4.3.1	Mean Trough (Predose) ($\pm$ SD) DC-806 Plasma Concentrations Versus Time on a Linear Scale	Cohort 1 PK	☐

Date: 08-Nov-2023

Output	Title	Analysis Set	Pre-Lock TFL
Figure 14.2.4.3.2	Mean Trough (Predose) (+SD) DC-806 Plasma Concentrations Versus Time on a Semi-Log Scale	Cohort 1 PK	☐
Figure 14.2.4.4.1	Mean Trough (Predose) ($\pm$ SD) DC-806 Plasma Concentrations Versus Time on a Linear Scale	Cohort 2 PK	☐
Figure 14.2.4.4.2	Mean Trough (Predose) (+SD) DC-806 Plasma Concentrations Versus Time on a Semi-Log Scale	Cohort 2 PK	☐
Figure 14.2.5.1	Box-and-Whisker Plots of Probe Substrates Plasma Pharmacokinetic Parameters	Cohort 1 PK	☐
Figure 14.2.5.2	Box-and-Whisker Plots of Probe Substrates Plasma Pharmacokinetic Parameters	Cohort 2 PK	☐
Figure 14.2.6.1.1	Individual Probe Substrates Plasma Concentrations Versus Time Overlaying Treatment Group on a Linear Scale	Cohort 1 PK	☐
Figure 14.2.6.1.2	Individual Probe Substrates Plasma Concentrations Versus Time Overlaying Treatment Group on a Semi-Log Scale	Cohort 1 PK	☐
Figure 14.2.6.2.1	Individual Probe Substrates Plasma Concentrations versus Time Overlaying Treatment Group on a Linear Scale	Cohort 2 PK	☐
Figure 14.2.6.2.2	Individual Probe Substrates Plasma Concentrations versus Time Overlaying Treatment Group on a Semi-Log Scale	Cohort 2 PK	☐
Figure 14.2.6.3.1	Individual DC-806 Plasma Concentrations versus Time on a Linear Scale	Cohort 1 PK	☐
Figure 14.2.6.3.2	Individual DC-806 Plasma Concentrations versus Time on a Semi-Log Scale	Cohort 1 PK	☐
Figure 14.2.6.4.1	Individual DC-806 Plasma Concentrations versus Time on a Linear Scale	Cohort 2 PK	☐
Figure 14.2.6.4.2	Individual DC-806 Plasma Concentrations versus Time on a Semi-Log Scale	Cohort 2 PK	☐
Figure 14.2.7.1	Spaghetti Plots of Individual Probe Substrates Plasma Concentrations Versus Time by Treatment	Cohort 1 PK	☐
Figure 14.2.7.2	Spaghetti Plots of Individual Probe Substrates Plasma Concentrations Versus Time by Treatment	Cohort 2 PK	☐
Figure 14.2.8.1	Scatter Plots of Individual Probe Substrates Plasma Pharmacokinetic Parameters	Cohort 1 PK	☐
Figure 14.2.8.2	Scatter Plots of Individual Probe Substrates Plasma Pharmacokinetic Parameters	Cohort 2 PK	☐
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	☒

Date: 08-Nov-2023

Output	Title	Analysis Set	Pre-Lock TFL
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 Shifts from Baseline	Safety	☒

Output	Title (Listings)	Pre-Lock TFL
<i>Section 16.2.1 – Disposition</i>		
Listing 16.2.1	Participant Disposition	☒
<i>Section 16.2.2 – Protocol Deviations</i>		
Listing 16.2.2	Important Protocol Deviations	☒
<i>Section 16.2.3 – Excluded Participants</i>		
Listing 16.2.3.1	Eligibility Criteria	☒
Listing 16.2.3.2	Analysis Sets	☒
<i>Section 16.2.4 – Demographics and Baseline Characteristics</i>		
Listing 16.2.4.1	Participant Demographics	☒
Listing 16.2.4.2	Serology Test Values at Screening	☒
Listing 16.2.4.3	Urine Alcohol and Drug Tests at Screening and Admission	☒
Listing 16.2.4.4	Medical History	☒
Listing 16.2.4.5	Prior and Concomitant Medications	☒
<i>Section 16.2.5 – Compliance</i>		
Listing 16.2.5	Study Drug Administration	☒
<i>Section 16.2.6 – Response Data</i>		
Listing 16.2.6.1	Individual Values of Plasma Concentrations – Cohort 1 DC-806/Midazolam + Repaglinide	☐
Listing 16.2.6.2	Individual Values of Plasma Concentrations – Cohort 2 DC-806/Digoxin + Rosuvastatin	☐
Listing 16.2.6.3	Individual Values of Plasma Pharmacokinetic Parameters – Cohort 1 DC-806/Midazolam + Repaglinide	☐
Listing 16.2.6.4	Individual Values of Plasma Pharmacokinetic Parameters – Cohort 2 DC-806/Digoxin + Rosuvastatin	☐

Date: 08-Nov-2023

Output	Title (Listings)	Pre-Lock TFL
Listing 16.2.6.5	Individual Values of Steady-State Plasma Pharmacokinetic Parameters for DC-806 – Cohort 1 DC-806/Midazolam + Repaglinide	☐
Listing 16.2.6.6	Individual Values of Steady-State Plasma Pharmacokinetic Parameters for DC-806– Cohort 2 DC-806/Digoxin + Rosuvastatin	☐
Listing 16.2.6.7	Plasma Pharmacokinetic Diagnostic Parameters – Cohort 1 DC-806/Midazolam + Repaglinide	☐
Listing 16.2.6.8	Plasma Pharmacokinetic Diagnostic Parameters – Cohort 2 DC-806/Digoxin + Rosuvastatin	☐
Listing 16.2.6.9	Individual Treatment Ratios of Pharmacokinetic Parameters – Cohort 1 DC-806/Midazolam + Repaglinide	☐
Listing 16.2.6.10	Individual Treatment Ratios of Pharmacokinetic Parameters - Cohort 2 DC-806/Digoxin + Rosuvastatin	☐
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	Adverse Events Leading to Study Discontinuation	☒
Listing 16.2.7.4	Listing of Serious Adverse Events	☒
Listing 16.2.7.5	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 Clinical Laboratory Results	☒
Section 16.2.9 Other Safety Data		
Listing 16.2.9	Vital Signs	☒
Listing 16.2.10.1	12-Lead Electrocardiogram Results	☒
Listing 16.2.10.2	Mean Triplicate 12-Lead Electrocardiogram Results	☒
Listing 16.2.11	Physical Examinations Findings	☒
Listing 16.2.12	Columbia-Suicide Severity Rating Scale Results - Cohort 1 DC-806/Midazolam + Repaglinide Only	☒

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 "DCE806104 Shells.pdf" to support the approved SAP.

Appendix 2: Parameter Definitions

Plasma Parameter Data Name	Plasma Parameter Protocol Name	Description	Analyte	Programming Notes
C _{max}	C _{max}	Maximum observed plasma concentration	Midazolam, 1-hydroxymidazolam, repaglinide, digoxin, rosuvastatin, and DC-806	C _{max} from WNL
T _{max}	t _{max}	Time to attain maximum observed plasma concentration	Midazolam, 1-hydroxymidazolam, repaglinide, digoxin, rosuvastatin, and DC-806	T _{max} from WNL
AUC _{last}	AUC _{0-t}	Area under the plasma concentration-time curve from time 0 to time t, where t is the last point with concentrations above the lower limit of quantification	Midazolam, 1-hydroxymidazolam, repaglinide, digoxin, rosuvastatin, and DC-806	AUC _{last} from WNL
AUC _{inf}	AUC _{0-inf}	Area under the plasma concentration-time curve from time 0 to infinity calculated as: $AUC_{0-inf} = AUC_{0-t} + C_{last}/k_{el}$, where C _{last} is the last measurable plasma concentration	Midazolam, 1-hydroxymidazolam, repaglinide, digoxin, rosuvastatin, and DC-806	AUC _{inf_obs} from WNL To be excluded from analysis/summaries if the following exclusion criteria are met: • Extrapolation, • Regression
T-HALF	t _{1/2}	Terminal elimination phase half-life, calculated as $0.693/k_{el}$	Midazolam, 1-hydroxymidazolam, repaglinide, digoxin, rosuvastatin, and DC-806	HL_Lambda_z from WNL To be excluded from analysis/summaries if any of the following exclusion criteria are met: • Extrapolation • Regression • Span



Plasma Parameter Data Name	Plasma Parameter Protocol Name	Description	Analyte	Programming Notes
CL/F	CL/F	Apparent oral clearance, calculated as dose/AUC _{0-inf}	Midazolam, 1-hydroxymidazolam, repaglinide, digoxin, rosuvastatin, and	CL_F_obs from VNL To be excluded from analysis/summaries if any of the following exclusion criteria are met: • Extrapolation, • Regression
Vz/F	Vz/F	Apparent volume of distribution at terminal phase	Midazolam, 1-hydroxymidazolam, repaglinide, digoxin, rosuvastatin, and	Vz_F_obs from VNL To be excluded from analysis/summaries if any of the following exclusion criteria are met: • Extrapolation, • Regression
C _{max,ss}	C _{max,ss}	Maximum observed plasma concentration at steady state (DC-806 only)	DC-806	C _{max} from VNL
C _{trough,ss}	C _{trough,ss}	Concentration observed at steady state immediately before the next dose is administered (DC-806 only)	DC-806	Predose concentration on Days 6, 7, & 8 for Cohort 1 and on Days 7, 8, & 9 for Cohort 2 from ADPC. Calculated in SAS.
AUC _{tau,ss}	AUC _{0-tau,ss}	Area under the plasma concentration-time curve over a dosing interval tau at steady state (DC-806 only)	DC-806	AUC _{tau} from VNL
T _{max,ss}	t _{max,ss}	Time to attain maximum observed plasma concentration at steady state (DC-806 only)	DC-806	T _{max} from VNL

Diagnostic Parameter	Description	SAS Programming Notes
AUC%Extrap	Percentage of AUC _{inf} due to extrapolation from the last quantifiable concentration observed to infinity.	AUC_%Extrap_obs from VNL
Adj Rsq	Goodness of fit statistic for the log-linear terminal elimination phase	Rsqr_adjusted from VNL



Lz (Protocol Name: k _e)	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

Appendix 3: Protocol Schedule of Assessments

Appendix 3.1 Schedule of Assessments – Cohort 1

Visit	Screening		Period 1				Period 2					Follow-up/ ET	
Study Day	-28 to -1	-1	1 Predose	1	2	3	4	5	6	7	8	9	5 (±2) days after collection of the last PK blood sample on Day 9 or time of ET
Confinement		X ^a	X	X	X	X	X	X	X	X	X		
Ambulatory	X												X
Admission		X											
Discharge												X ^b	
Informed Consent	X												
Medical and Surgical History	X	X											
Demographics	X												
Physical Examination ^c	X												X
Body Weight and BMI	X	X											
Height	X												
Serology (HBsAg, anti-HCV, anti-HIV 1 and 2)	X												
C-SSRS	X												
Drug and Alcohol Screen	X	X											
Pregnancy Test (for all females)	X	X											X
FSH Test (postmenopausal females only)	X												
Clinical Laboratory ^d	X	X	X				X				X	X	X
Blood Glucose Monitoring				X						X			
Post Repaglinide Dosing ^e									X	X			X
12-Lead ECG ^{f,g}	X		X	X						X	X		X
Vital Signs ^h	X		X		X					X	X		
Continuous Pulse Oximetry				X						X			
Post Midazolam Dosing ⁱ													
Eligibility Check	X	X	X										

TEM-02021 8.0 Effective Date:

Strictly Confidential. © 2023, ICON. All rights reserved.

Page 25 of 33



Visit	Screening	Period 1					Period 2					Follow-up/ ET
Study Day	-28 to -1	-1	1 Predose	2	3	4	5	6	7	8	9	5 (±2) days after collection of the last PK blood sample on Day 9 or time of ET
Midazolam/Repaglinide Probe Substrate Cocktail Dosing ^j			X						X			
DC-806 BID Dosing ^k						X	X	X	X	X		
Blood Sampling for PK ^l		See Appendix 3.3 and Appendix 3.4										
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X
AE Monitoring ^{m, n}	X	X	X ^o	X	X	X	X	X	X ^o	X	X	X

See Appendix 3.3 and Appendix 3.4

AE=adverse event; BMI=body mass index; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET= early termination; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; min=minutes; PK=pharmacokinetic(s); SAEs=serious adverse events

- Confinement on Day -1.
- Participants will be discharged from the clinical site on Day 9 after the last PK sampling.
- 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 on Day 9, per the Investigator's discretion.
- Clinical laboratory tests (including clinical chemistry, hematology, coagulation, and urinalysis): at screening, on Day -1 (admission), predose on Days 1, and 4, on Day 8 and Day 9 (discharge) and at follow-up/ET.
- Blood glucose test every 30 minutes from 0.5 hours to 4 hours post repaglinide dose on Day 1 and Day 7.
- Single 12-lead ECG measurements will be taken (after the participant has rested in the supine position for at least 5 minutes) at screening, pre-probe substrate dose and 2 hours post probe substrate dose on Day 7; and at follow-up/ET.
- Triplicate 12-lead ECG will be performed on Day 1 (predose), and predose and 2 hours post DC-806 morning dose on Day 6. Each triplicate recording will be separated by at least 30 seconds. Postdose ECGs will be performed ±15 min from scheduled timepoint. Safety assessment and PK sampling need to be performed after the triplicate ECG assessment.
- Vital signs (supine systolic blood pressure, diastolic blood pressure, pulse rate, pulse oximetry, body temperature and respiratory rate) will be obtained after at least 5 min at rest at screening and within 60 minutes prior to initial 2-probe substrate cocktail administration on Day 1, and at 1, 2, 4, 6, 12 and 24 hours after initial 2-probe substrate cocktail administration on Day 1, and within 60 minutes prior to 2nd dose of probe substrate cocktail administration on Day 7 and at 1, 2, 6, 12, and 24 hours after 2nd dose of 2--probe substrate cocktail administration of Day 7, and at follow-up/ET. Vital signs may be collected ±10 min from scheduled timepoint. When vital sign collection timepoints coincide with PK collection timepoints, vital signs will be collected first and PK samples will be collected as scheduled.
- Continuous measuring of pulse oximetry and respiratory rate through 6 hours post midazolam dosing on Day 1 and Day 7.
- Midazolam and repaglinide will be administered as a 2-probe substrate cocktail under fasted conditions. The time of dosing needs to be approximately the same in both periods 1 and 2. In Period 2, the 2-probe substrate cocktail of midazolam and repaglinide will be administered under fasted conditions in the morning of Day 7, 1.5 hour (± 15 minutes) after the DC-806 dose.
- DC-806 will be administered once every 12 hours (±30 minutes) starting the morning of Day 4. The final DC-806 dose will be given at night on Day 8. DC-806 doses will be administered under fed conditions with the exception that fasting is required for the DC-806 morning dose on the day when the probe substrate cocktails are dosed.

Date: 08-Nov-2023

- l. Please refer to Tables 3 and 4 for details.
 - m. After informed consent has been obtained but prior to initiation of study drugs, only SAEs caused by a protocol-mandated intervention should be collected and reported to the Sponsor. After initiation of study drugs, all AEs will be collected and reported to the Sponsor 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(s).
 - n. For Cohort 1 since midazolam is being administered which is known to cause transient drowsiness, midazolam monitoring will include assessment of alertness/sedation at the discretion of the Investigator. Pulse oximetry and respiratory rate will be measured on Day 1 and Day 7 post midazolam dosing.
- Note: If multiple assessments are scheduled for the same timepoint, procedures should be performed in the following sequence: ECG, vital signs, blood.

Appendix 3.2 Schedule of Assessments – Cohort 2

Visit	Screening	Period 1						Period 2						Follow-up/ ET	
Study Day	-28 to -1	1 Predose	1	2	3	4	5	6	7	8	9	10	11	12	8 (±2) days after collection of the last PK blood sample on Day 12 or time of ET
Confinement		X	X	X	X	X	X	X	X	X	X	X	X		X
Ambulatory	X														
Admission	X														
Discharge													X ^b		
Informed Consent	X														
Medical and Surgical History	X														
Demographics	X														X
Physical Examination ^c	X														
Body Weight and BMI	X	X													
Height	X														
Serology (HBsAg, anti- HCV, anti-HIV 1 and 2)	X														
Drug and Alcohol Screen	X														X
Pregnancy Test (for all females)	X	X													
FSH Test (postmenopausal females only)	X														
Clinical Laboratory ^d	X	X		X	X		X	X			X	X		X	X
12-Lead ECG ^{e,f}	X	X							X	X	X				X
Vital Signs ^g	X	X	X	X						X	X				
Eligibility Check	X	X													
Digoxin/Rosuva- statin Probe Substrate Cocktail Dosing ^h			X							X					
DC-806 BID Dosing ⁱ							X	X	X	X	X				

TEM-02021 8.0 Effective Date:

Strictly Confidential. © 2023, ICON. All rights reserved.

Page 28 of 33



Visit	Screening	Period 1					Period 2					Follow-up/ ET			
Study Day	-28 to -1	1 Predose	1	2	3	4	5	6	7	8	9	10	11	12	8 (±2) days after collection of the last pPK blood sample on Day 12 or time of ET
Blood Sampling for PK _j		-1	See Appendix 3.5 and Appendix 3.6												
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Monitoring ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

See Appendix 3.5 and Appendix 3.6

AE=adverse event; BMI=body mass index; ECG=electrocardiogram; ET=early termination; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; min=minutes; PK=pharmacokinetic(s)

- Confinement on Day -1.
- Participants will be discharged from the clinic site on Day 12 after the last PK sampling.
- Complete physical examinations will be conducted at screening and follow-up/ET. Symptom driven physical examinations may be conducted at any time, per the Investigator's discretion.
- Clinical laboratory tests (including clinical chemistry, hematology, coagulation, and urinalysis): at screening, on Day -1 (admission), on Day 1 (predose), Day 2, Day 3, Day 5 (predose), Day 9, Day 10, and Day 12 (discharge) and follow-up/ET.
- Single 12-lead ECG measurements will be taken (after the participant has rested in the supine position for at least 5 minutes) at screening; preprobe substrate dose, 2 hours, and 6 hours post probe substrate dose on Day 8; predose on Day 9; and at follow-up/ET.
- Triplicate 12-lead ECG will be performed on Day 1 (predose), and predose and 2 hours post- DC-806 morning dose on Day 7. Each triplicate recording will be separated by at least 30 seconds. Postdose ECGs will be performed ±15 min from scheduled timepoint. Safety assessment and PK sampling need to be performed after the triplicate ECG assessment.
- Vital signs (supine systolic blood pressure, diastolic blood pressure, pulse rate, body temperature and respiratory rate) will be obtained after at least 5 min at rest in the supine position at screening and within 60 minutes prior to initial 2-probe substrate cocktail administration on Day 1, and at 1, 2, 6, 12 and 24 hours after initial 2-probe substrate cocktail administration on Day 1, and within 60 minutes prior to 2nd dose of probe substrate cocktail administration on Day 8 and at 1, 2, 6, 12, and 24 hours after 2nd dose of 2-probe cocktail administration of Day 8, and at follow-up/ET. Vital signs may be collected ±10 min from scheduled timepoint. When vital sign collection timepoints coincide with PK collection timepoints, vital signs will be collected first and PK samples will be collected as scheduled.
- Digoxin and rosuvastatin will be administered as a 2-probe substrate cocktail under fasted conditions. The time of dosing needs to be approximately the same in both periods 1 and 2. In Period 2, the 2-probe substrate cocktail of digoxin and rosuvastatin will be administered under fasted conditions in the morning of Day 8 at 1.5 hour (± 15 minutes) after the DC-806 dose.
- DC-806 will be administered once every 12 hours (±30 minutes) under fed conditions starting in the morning of Day 5, with the exception that fasting is required for the DC-806 morning dose on the day when the probe substrate cocktails are dosed. The final DC-806 dose will be given in the evening on Day 9.
- Please refer to Tables 5 and 6 for details.
- After informed consent has been obtained but prior to initiation of study drugs, only SAEs caused by a protocol-mandated intervention should be collected and reported to the Sponsor. After initiation of study drugs, all adverse events will be collected and reported to the Sponsor 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(s).

Note: If multiple assessments are scheduled for the same timepoint, procedures should be performed in the following sequence: ECG, vital signs, blood.

Appendix 3.3 Schedule of Sampling for PK Assessments for Probe Substrates (Cohort 1)

Study Day	Day 1 (Period 1) and Day 7 (Period 2)														2/8	3/9
	Nominal Timepoint (hours) for Probe Substrates	0 Predose	0.25	0.5	0.75	1	1.5	2	3	4	6	8	10	12		
Midazolam/ 1-hydroxymidazolam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Repaglinide		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Note: For sampling purposes probe substrate dosing time is 1.5 hours after DC-806 dosing, and probe substrate dosing time is defined as time=0.

Note: PK sampling time windows: predose sample: within 30 minutes of dosing; <4 hours after study drug (probe substrates or DC-806) administration: ±5 minutes; ≥4 and <24 hours after study drug administration: ±10 minutes, and ≥24 hours after study drug administration: ±60 minutes.

Appendix 3.4 Schedule of Sampling for PK Assessments for DC-806 (Cohort 1)

Study Day	Day 6 morning (Period 2)		Day 7 morning (Period 2)										Day 8 morning		
	0 Predose (-1.5)	2 (0.5)	0 Predose (-1.5)	0.5 (-1.0)	0.75 (-0.75)	1 (-0.5)	1.5 (0)	2 (0.5)	3 (1.5)	4 (2.5)	6 (4.5)	8 (6.5)	10 (8.5)	12 (10.5)	0 Predose (-1.5)
DC-806	X ^a	X	X ^a	X		X		X		X		X		X ^a	X ^a

a. PK sampling prior to DC-806 dosing

Note: All timepoints (in parentheses) for DC-806 PK sampling are relative to probe substrate dosing time (i.e., the current nominal DC-806 sampling time minus 1.5 hours).

Note: PK sampling time windows: predose samples: within 30 minutes of dosing; <4 hours after study drug (DC-806) administration: ±5 minutes; ≥4 hours after study drug administration: ±10 minutes.



Appendix 3.5 Schedule of Sampling for PK Assessments for Probe Substrates (Cohort 2)

Study Day	Day 1 (Period 1) and Day 8 (Period 2)																2/9	3/10	4/11	5/12
	Nominal Timepoint (hours) for Probe Substrates	0 Predose	0.25	0.5	0.75	1	1.5	2	3	4	6	8	10	12						
Digoxin		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Rosuvastatin		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Note: For sampling purposes substrate dosing time is 1.5 hours after DC-806 dosing, and probe substrate dosing time is defined as time=0.

Note: PK sampling time windows: predose samples: within 30 minutes of dosing; <4 hours after study drug (probe substrates or DC-806) administration: ±5 minutes; ≥4 and <24 hours after study drug administration: ±10 minutes, and ≥24 hours after study drug administration: ±60 minutes.

Appendix 3.6 Schedule of Sampling for PK Assessments for DC-806 (Cohort 2)

Study Day	Day 7 morning (Period 2)										Day 8 morning (Period 2)										Day 9 morning	
	Nominal Timepoint (hours) for DC-806	0	Predose	2	0	0.5	0.75	1	1.5	2	3	4	6	8	10	12	24	48	72	96	0	Predose (-1.5)
DC-806		X ^a	X	X	X ^a	X	X	X	X	X	X	X	X	X	X	X ^a	X	X	X	X	X ^a	X ^a

a. PK sampling prior to DC-806 dosing

Note: All timepoints (in parentheses) for DC-806 PK sampling are relative to probe substrate dosing time (i.e. the current nominal DC-806 sampling time minus 1.5 hours.

Note: PK sampling time windows: predose samples: within 30 minutes of dosing; <4 hours after study drug (DC-806) administration: ±5 minutes; ≥4 hours after study drug administration: ±10 minutes.

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
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
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
WNL	WinNonlin

14.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes
24-Oct-2023	PPD	Draft SAP Version 1
08-Nov-2023		Draft SAP Version 2

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Alpha-hydroxymidazolam Parameter=AUClast (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Midazolam + Repaglinide Midazolam + Repaglinide

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	28

Number of Observations	
Number of Observations Read	28
Number of Observations Used	28
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 Category 1=Alpha-hydroxymidazolam Parameter=AUClast (h*ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	51.98724660		
1	1	30.60821177	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.3171
Residual	0.03591

Fit Statistics	
-2 Res Log Likelihood	30.6
AIC (Smaller is Better)	34.6
AICC (Smaller is Better)	35.1
BIC (Smaller is Better)	35.9

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Alpha-hydroxymidazolam Parameter=AUClast (h*ng/mL)

Type 3 Tests of Fixed
Effects

NumDen			
Effect	DF	DF F	ValuePr > F
TRTP	1	13	34.47<.0001

Coefficients for DC-806 + Midazolam + Repaglinide vs
Midazolam + Repaglinide

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Midazolam + Repaglinide	1
TRTP	Midazolam + Repaglinide	-1

Estimates

Label	Standard			
	Estimate	ErrorDF	t	ValuePr > t Alpha Lower Upper
DC-806 + Midazolam + Repaglinide vs Midazolam + Repaglinide	0.4205	0.0716213	5.87	<.0001 0.10.29360.5473

Least Squares Means

EffectPlanned Treatment		Standard			
TRTP	DC-806 + Midazolam + Repaglinide	Estimate	ErrorDF	t	ValuePr > t Alpha Lower Upper
		2.0393	0.158813	12.84	<.0001 0.11.75812.3205
TRTP	Midazolam + Repaglinide	Estimate	ErrorDF	t	ValuePr > t Alpha Lower Upper
		1.6188	0.158813	10.20	<.0001 0.11.33761.9000

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Alpha-hydroxymidazolam Parameter=Cmax (ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Midazolam + Repaglinide Midazolam + Repaglinide

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	I
Max Obs per Subject	28

Number of Observations	
Number of Observations Read	28
Number of Observations Used	28
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 Category 1=Alpha-hydroxymidazolam Parameter=Cmax (ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	37.63263678		
1	1	36.77259579	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.05142
Residual	0.1518

Fit Statistics	
-2 Res Log Likelihood	36.8
AIC (Smaller is Better)	40.8
AICC (Smaller is Better)	41.3
BIC (Smaller is Better)	42.1

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Alpha-hydroxymidazolam Parameter=Cmax (ng/mL)

Type 3 Tests of Fixed
Effects

NumDen		
Effect	DF	ValuePr > F
TRTP	1 13	0.000.9832

Coefficients for DC-806 + Midazolam + Repaglinide vs
Midazolam + Repaglinide

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Midazolam + Repaglinide	1
TRTP	Midazolam + Repaglinide	-1

Estimates

Label	Standard			
	Estimate	ErrorDFt	ValuePr > t Alpha	Lower Upper
DC-806 + Midazolam + Repaglinide vs Midazolam + Repaglinide	0.003153	0.147313	0.02 0.9832	0.1 -0.25760.2639

Least Squares Means

EffectPlanned Treatment	Standard			
	Estimate	ErrorDFt	ValuePr > t Alpha	Lower Upper
TRTP DC-806 + Midazolam + Repaglinide	1.0817	0.120513	8.98 <.0001	0.10.86831.2950
TRTP Midazolam + Repaglinide	1.0785	0.120513	8.95 <.0001	0.10.86511.2919

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Midazolam Parameter=AUCinf (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues	
TRTP	2DC-806 + Midazolam + Repaglinide Midazolam + Repaglinide
SUBJID	CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	1
Subjects	1
Max Obs per Subject	14

Number of Observations	
Number of Observations Read	14
Number of Observations Used	14
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 Category 1=Midazolam Parameter=AUCinf (h*ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	10.21709971		
1	1	7.13430532	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.06287
Residual	0.03632

Fit Statistics	
-2 Res Log Likelihood	7.1
AIC (Smaller is Better)	11.1
AICC (Smaller is Better)	12.5
BIC (Smaller is Better)	11.0

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Midazolam Parameter=AUCinf (h*ng/mL)

Type 3 Tests of Fixed
Effects

NumDen			
Effect	DF	DF	ValuePr > F
TRTP	1	6	207.62<.0001

Coefficients for DC-806 + Midazolam + Repaglinide vs
Midazolam + Repaglinide

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Midazolam + Repaglinide	1
TRTP	Midazolam + Repaglinide	-1

Estimates

Label	Standard			
	Estimate	ErrorDF	t ValuePr > t	Alpha Lower Upper
DC-806 + Midazolam + Repaglinide vs Midazolam + Repaglinide	1.4677	0.1019	6	14.41 <.0001 0.11.26981.6657

Least Squares Means

EffectPlanned Treatment	Standard			
	Estimate	ErrorDF	t ValuePr > t	Alpha Lower Upper
TRTP DC-806 + Midazolam + Repaglinide	4.5738	0.1190	6	38.42 <.0001 0.14.34254.8051
TRTP Midazolam + Repaglinide	3.1061	0.1190	6	26.09 <.0001 0.12.87483.3374

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Midazolam Parameter=AUClast (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Midazolam + Repaglinide Midazolam + Repaglinide

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	28

Number of Observations	
Number of Observations Read	28
Number of Observations Used	28
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 Category 1=Midazolam Parameter=AUClast (h*ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	18.83454272		
1	1	11.58656856	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.06447
Residual	0.03415

Fit Statistics	
-2 Res Log Likelihood	11.6
AIC (Smaller is Better)	15.6
AICC (Smaller is Better)	16.1
BIC (Smaller is Better)	16.9

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Midazolam Parameter=AUClast (h*ng/mL)

Type 3 Tests of Fixed
Effects

NumDen			
Effect	DF	DF F	ValuePr > F
TRTP	1	13	461.50<.0001

Coefficients for DC-806 + Midazolam + Repaglinide vs
Midazolam + Repaglinide

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Midazolam + Repaglinide	1
TRTP	Midazolam + Repaglinide	-1

Estimates

Label	Standard			
	Estimate	ErrorDF	t ValuePr > t	Alpha Lower Upper
DC-806 + Midazolam + Repaglinide vs Midazolam + Repaglinide	1.5004	0.0698413	21.48	<.0001 0.11.37671.6241

Least Squares Means

EffectPlanned Treatment	Standard			
	Estimate	ErrorDF	t ValuePr > t	Alpha Lower Upper
TRTP DC-806 + Midazolam + Repaglinide	4.4136	0.0839313	52.59	<.0001 0.14.26504.5623
TRTP Midazolam + Repaglinide	2.9132	0.0839313	34.71	<.0001 0.12.76463.0618

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Midazolam Parameter=Cmax (ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Midazolam + Repaglinide Midazolam + Repaglinide

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	28

Number of Observations	
Number of Observations Read	28
Number of Observations Used	28
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 Category 1=Midazolam Parameter=Cmax (ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	18.24155823		
1	1	13.31828264	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.05412
Residual	0.04227

Fit Statistics	
-2 Res Log Likelihood	13.3
AIC (Smaller is Better)	17.3
AICC (Smaller is Better)	17.8
BIC (Smaller is Better)	18.6

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Midazolam Parameter=Cmax (ng/mL)

Type 3 Tests of Fixed
Effects

NumDen			
Effect	DF	DF F	ValuePr > F
TRTP	1	13	201.75<.0001

Coefficients for DC-806 + Midazolam + Repaglinide vs
Midazolam + Repaglinide

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Midazolam + Repaglinide	1
TRTP	Midazolam + Repaglinide	-1

Estimates

Label	Standard			
	Estimate	ErrorDFt	ValuePr > t	Alpha Lower Upper
DC-806 + Midazolam + Repaglinide vs Midazolam + Repaglinide	1.1038	0.0777113	14.20	<.0001 0.10.96621.2414

Least Squares Means

EffectPlanned Treatment	Standard			
	Estimate	ErrorDFt	ValuePr > t	Alpha Lower Upper
TRTP DC-806 + Midazolam + Repaglinide	3.2162	0.0829813	38.76	<.0001 0.13.06933.3632
TRTP Midazolam + Repaglinide	2.1124	0.0829813	25.46	<.0001 0.11.96552.2594

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Repaglinide Parameter=AUCinf (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues	
TRTP	2DC-806 + Midazolam + Repaglinide Midazolam + Repaglinide
SUBJID	CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	1
Subjects	1
Max Obs per Subject	6

Number of Observations	
Number of Observations Read	6
Number of Observations Used	6
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 Category 1=Repaglinide Parameter=AUCinf (h*ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	6.59550311		
1	1	1.93081379	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.1671
Residual	0.008751

Fit Statistics	
-2 Res Log Likelihood	1.9
AIC (Smaller is Better)	5.9
AICC (Smaller is Better)	17.9
BIC (Smaller is Better)	4.1

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Repaglinide Parameter=AUCinf (h*ng/mL)

Type 3 Tests of Fixed
Effects

NumDen			
Effect	DF	DF	ValuePr > F
TRTP	1	2	125.230.0079

Coefficients for DC-806 + Midazolam + Repaglinide vs
Midazolam + Repaglinide

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Midazolam + Repaglinide	1
TRTP	Midazolam + Repaglinide	-1

Estimates

Label	Standard			
	Estimate	ErrorDFt	ValuePr > t	Alpha Lower Upper
DC-806 + Midazolam + Repaglinide vs Midazolam + Repaglinide	0.8548	0.07638	2	11.19 0.0079 0.10.63171.0778

Least Squares Means

EffectPlanned Treatment	Standard			
	Estimate	ErrorDFt	ValuePr > t	Alpha Lower Upper
TRTP DC-806 + Midazolam + Repaglinide	3.2337	0.2421	2	13.36 0.0056 0.12.52683.9406
TRTP Midazolam + Repaglinide	2.3789	0.2421	2	9.83 0.0102 0.11.67203.0858

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Repaglinide Parameter=AUClast (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Midazolam + Repaglinide Midazolam + Repaglinide

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	28

Number of Observations	
Number of Observations Read	28
Number of Observations Used	28
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 Category 1=Repaglinide Parameter=AUClast (h*ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	41.44574966		
1	1	25.32865074	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.1984
Residual	0.03696

Fit Statistics	
-2 Res Log Likelihood	25.3
AIC (Smaller is Better)	29.3
AICC (Smaller is Better)	29.9
BIC (Smaller is Better)	30.6

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Repaglinide Parameter=AUClast (h*ng/mL)

Type 3 Tests of Fixed
Effects

NumDen		
Effect	DF	ValuePr > F
TRTP	1 13	104.84<.0001

Coefficients for DC-806 + Midazolam + Repaglinide vs
Midazolam + Repaglinide

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Midazolam + Repaglinide	1
TRTP	Midazolam + Repaglinide	-1

Estimates

Label	Standard			
	Estimate	ErrorDFt	ValuePr > t	Alpha Lower Upper
DC-806 + Midazolam + Repaglinide vs Midazolam + Repaglinide	0.7440	0.0726613	10.24	<.0001 0.10.61530.8727

Least Squares Means

EffectPlanned Treatment		Standard			
Effect	Planned Treatment	Estimate	ErrorDFt	ValuePr > t	Alpha Lower Upper
		Estimate	ErrorDFt	ValuePr > t	Alpha Lower Upper
TRTP	DC-806 + Midazolam + Repaglinide	3.3307	0.129613	25.69	<.0001 0.13.10113.5603
TRTP	Midazolam + Repaglinide	2.5867	0.129613	19.95	<.0001 0.12.35712.8163

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Repaglinide Parameter=Cmax (ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Midazolam + Repaglinide Midazolam + Repaglinide

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	28

Number of Observations	
Number of Observations Read	28
Number of Observations Used	28
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 Category 1=Repaglinide Parameter=Cmax (ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	39.78206564		
1	1	32.69543435	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.1431
Residual	0.07764

Fit Statistics	
-2 Res Log Likelihood	32.7
AIC (Smaller is Better)	36.7
AICC (Smaller is Better)	37.2
BIC (Smaller is Better)	38.0

Appendix 16.1.9.2.1
Statistical Methods and Analysis Output
Supporting Table 14.2.3.1

The Mixed Procedure

Parameter Category 1=Repaglinide Parameter=Cmax (ng/mL)

Type 3 Tests of Fixed
Effects

NumDen	
Effect	DF
TRTP	1 13
	35.51 <.0001

Coefficients for DC-806 + Midazolam + Repaglinide vs
Midazolam + Repaglinide

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Midazolam + Repaglinide	1
TRTP	Midazolam + Repaglinide	-1

Estimates

Label	Standard	
	Estimate	ErrorDFt ValuePr > t Alpha Lower Upper
DC-806 + Midazolam + Repaglinide vs Midazolam + Repaglinide	0.6276	0.105313 5.96 <.0001 0.10.44110.8141

Least Squares Means

Standard	
EffectPlanned Treatment	Estimate ErrorDFt ValuePr > t Alpha Lower Upper
TRTP DC-806 + Midazolam + Repaglinide	2.6663 0.125613 21.23 <.0001 0.12.44392.8886
TRTP Midazolam + Repaglinide	2.0386 0.125613 16.24 <.0001 0.11.81632.2610

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=AUClast (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	I
Max Obs per Subject	26

Number of Observations	
Number of Observations Read	26
Number of Observations Used	26
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 Category 1=Digoxin Parameter=AUClast (h*ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	31.01205509		
1	1	30.94059436	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.01326
Residual	0.1589

Fit Statistics	
-2 Res Log Likelihood	30.9
AIC (Smaller is Better)	34.9
AICC (Smaller is Better)	35.5
BIC (Smaller is Better)	36.1

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=AUClast (h*ng/mL)

Type 3 Tests of Fixed
Effects

		NumDen	
Effect	DF	DF	ValuePr > F
TRTP	1	12	0.320.5797

Coefficients for DC-806 + Digoxin + Rosuvastatin vs
Digoxin + Rosuvastatin

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Digoxin + Rosuvastatin	1
TRTP	Digoxin + Rosuvastatin	-1

Estimates

Label	Standard		ErrorDFt	ValuePr > t Alpha	Lower	Upper
	Estimate					
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	0.08900	0.156312	0.57	0.5797	0.1	-0.18960.3676

Least Squares Means

		Standard	
Effect	Planned Treatment	Estimate	ErrorDFt
DC-806 + Digoxin + Rosuvastatin		2.7320	0.115112
TRTP	DC-806 + Digoxin + Rosuvastatin	2.7320	0.115112
TRTP	Digoxin + Rosuvastatin	2.6430	0.115112

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=Cmax (ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	I
Max Obs per Subject	26

Number of Observations	
Number of Observations Read	26
Number of Observations Used	26
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 Category 1=Digoxin Parameter=Cmax (ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	9.16487800		
1	1	7.91606486	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.02178
Residual	0.04749

Fit Statistics	
-2 Res Log Likelihood	7.9
AIC (Smaller is Better)	11.9
AICC (Smaller is Better)	12.5
BIC (Smaller is Better)	13.0

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=Cmax (ng/mL)

Type 3 Tests of Fixed
Effects

		NumDen	
Effect	DF	DF	ValuePr > F
TRTP	1	12	18.710.0010

Coefficients for DC-806 + Digoxin + Rosuvastatin vs
Digoxin + Rosuvastatin

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Digoxin + Rosuvastatin	1
TRTP	Digoxin + Rosuvastatin	-1

Estimates

Label	Standard	
	Estimate	ErrorDF t ValuePr > t Alpha Lower Upper
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	0.3697	0.0854812 4.33 0.0010 0.10.21740.5221

Least Squares Means

		Standard	
Effect	Planned Treatment	Estimate	ErrorDF t ValuePr > t Alpha Lower Upper
TRTP	DC-806 + Digoxin + Rosuvastatin	0.3271	0.0730012 4.48 0.0008 0.1 0.1970 0.4572
TRTP	Digoxin + Rosuvastatin	-0.04266	0.0730012 -0.58 0.5698 0.1-0.17280.08744

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=AUCinf (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues	
TRTP	2 DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin
SUBJID	CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	20

Number of Observations	
Number of Observations Read	20
Number of Observations Used	20
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 Category 1=Rosuvastatin Parameter=AUCinf (h*ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	14.16675553		
1	1	11.37939708	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.05140
Residual	0.04819

Fit Statistics	
-2 Res Log Likelihood	11.4
AIC (Smaller is Better)	15.4
AICC (Smaller is Better)	16.2
BIC (Smaller is Better)	16.0

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=AUCinf (h*ng/mL)

Type 3 Tests of Fixed
Effects

NumDen	
Effect	DF
TRTP	1
	9
	0.350.5704

Coefficients for DC-806 + Digoxin + Rosuvastatin vs
Digoxin + Rosuvastatin

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Digoxin + Rosuvastatin	1
TRTP	Digoxin + Rosuvastatin	-1

Estimates

Label	Standard			
	Estimate	ErrorDFt	ValuePr > t Alpha	Lower Upper
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	-0.05782	0.09818	9	-0.59 0.5704 0.1 -0.23780.1221

Least Squares Means

Least Squares Means	
Standard	
EffectPlanned Treatment	ErrorDFt ValuePr > t Alpha Lower Upper
TRTP DC-806 + Digoxin + Rosuvastatin	3.1389 0.09980 9 31.45 <.0001 0.12.95603.3219
TRTP Digoxin + Rosuvastatin	3.1967 0.09980 9 32.03 <.0001 0.13.01383.3797

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure
Parameter Category 1=Rosuvastatin Parameter=AUClast (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues	
TRTP	2DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin
SUBJID	CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	26

Number of Observations	
Number of Observations Read	26
Number of Observations Used	26
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 Category 1=Rosuvastatin Parameter=AUClast (h*ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	40.56746549		
1	1	29.64636949	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.1981
Residual	0.05819

Fit Statistics	
-2 Res Log Likelihood	29.6
AIC (Smaller is Better)	33.6
AICC (Smaller is Better)	34.2
BIC (Smaller is Better)	34.8

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure
Parameter Category 1=Rosuvastatin Parameter=AUClast (h*ng/mL)

Type 3 Tests of Fixed Effects			
NumDen			
Effect	DF	DF	ValuePr > F
TRTP	1	12	2.880.1155

Coefficients for DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin			
Effect	Planned Treatment	Row1	
Intercept			
TRTP	DC-806 + Digoxin + Rosuvastatin	1	
TRTP	Digoxin + Rosuvastatin	-1	

Label	Estimates			
	Estimate	Standard Error	DFt	ValuePr > t Alpha Lower Upper
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	-0.1605	0.0946212	-1.70	0.1155 0.1 -0.3291 0.008114

Least Squares Means			
Standard			
Effect	Planned Treatment	Estimate	ErrorDFt ValuePr > t Alpha Lower Upper
TRTP	DC-806 + Digoxin + Rosuvastatin	3.2335	0.140412 23.03 <.0001 0.12.98333.4838
TRTP	Digoxin + Rosuvastatin	3.3941	0.140412 24.17 <.0001 0.13.14383.6443

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=Cmax (ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class Levels/Values	
TRTP	2DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin
SUBJID	CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	I
Max Obs per Subject	26

Number of Observations	
Number of Observations Read	26
Number of Observations Used	26
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 Category 1=Rosuvastatin Parameter=Cmax (ng/mL)

Iteration History				
Iteration	Evaluations	-2 Res	Log Like	Criterion
0	1	1	51.45208238	
1	1	1	48.58664179	0.00000000

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.1859
Residual	0.2175

Fit Statistics	
-2 Res Log Likelihood	48.6
AIC (Smaller is Better)	52.6
AICC (Smaller is Better)	53.2
BIC (Smaller is Better)	53.7

Appendix 16.1.9.2.2
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=Cmax (ng/mL)

Type 3 Tests of Fixed Effects			
NumDen			
Effect	DF	DF F	ValuePr > F
TRTP	1	12	0.290.5982

Coefficients for DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Digoxin + Rosuvastatin	1
TRTP	Digoxin + Rosuvastatin	-1

Estimates

Label	Standard			
	Estimate	ErrorDFt	ValuePr > t Alpha	Lower Upper
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	-0.09902	0.182912	-0.54	0.5982 0.1 -0.42500.2270

Least Squares Means

EffectPlanned Treatment		Standard			
		Estimate	ErrorDFt	ValuePr > t Alpha	Lower Upper
TRTP	DC-806 + Digoxin + Rosuvastatin	0.9648	0.176212	5.48	0.0001 0.10.65091.2788
TRTP	Digoxin + Rosuvastatin	1.0638	0.176212	6.04	<.0001 0.10.74991.3778

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=AUClast (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	24

Number of Observations	
Number of Observations Read	24
Number of Observations Used	24
Number of Observations Not Used	0

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=AUClast (h*ng/mL)

Iteration History				
Iteration	Evaluations	-2 Res	Log Like	Criterion
0	1	1	3.40525492	
1	1	1	1.67931950	0.00000000

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.02078
Residual	0.03375

Fit Statistics	
-2 Res Log Likelihood	1.7
AIC (Smaller is Better)	5.7
AICC (Smaller is Better)	6.3
BIC (Smaller is Better)	6.6

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=AUClast (h*ng/mL)

Type 3 Tests of Fixed Effects			
NumDen			
Effect	DF	DF F	ValuePr > F
TRTP	1	11	9.350.0109

Coefficients for DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin			
Effect	Planned Treatment	Row1	
Intercept			
TRTP	DC-806 + Digoxin + Rosuvastatin	1	
TRTP	Digoxin + Rosuvastatin	-1	

Label	Estimates			
	Estimate	Standard Error	DFt	ValuePr > t Alpha
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	0.2293	0.07500	11	3.06 0.0109 0.10.09460 0.3640

Least Squares Means			
Standard			
Effect	Planned Treatment	Estimate	ErrorDFt ValuePr > t Alpha Lower Upper
TRTP	DC-806 + Digoxin + Rosuvastatin	2.8690	0.0674111 42.56 <.0001 0.12.74802.9901
TRTP	Digoxin + Rosuvastatin	2.6397	0.0674111 39.16 <.0001 0.12.51872.7608

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=Cmax (ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	26

Number of Observations	
Number of Observations Read	26
Number of Observations Used	26
Number of Observations Not Used	0

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=Cmax (ng/mL)

Iteration History				
Iteration	Evaluations	-2 Res	Log Like	Criterion
0	1		9.16487800	
1	1		7.91606486	0.00000000

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.02178
Residual	0.04749

Fit Statistics	
-2 Res Log Likelihood	7.9
AIC (Smaller is Better)	11.9
AICC (Smaller is Better)	12.5
BIC (Smaller is Better)	13.0

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Digoxin Parameter=Cmax (ng/mL)

Type 3 Tests of Fixed
Effects

		NumDen	
Effect	DF	DF	ValuePr > F
TRTP	1	12	18.710.0010

Coefficients for DC-806 + Digoxin + Rosuvastatin vs
Digoxin + Rosuvastatin

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Digoxin + Rosuvastatin	1
TRTP	Digoxin + Rosuvastatin	-1

Estimates

Label	Standard		
	Estimate	ErrorDFt	ValuePr > t Alpha Lower Upper
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	0.3697	0.0854812	4.33 0.0010 0.10.21740.5221

Least Squares Means

		Standard	
EffectPlanned Treatment	Estimate	ErrorDFt	ValuePr > t Alpha Lower Upper
TRTP DC-806 + Digoxin + Rosuvastatin	0.3271	0.0730012	4.48 0.0008 0.1 0.1970 0.4572
TRTP Digoxin + Rosuvastatin	-0.04266	0.0730012	-0.58 0.5698 0.1-0.17280.08744

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=AUCinf (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues	
TRTP	2DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin
SUBJID	CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	20

Number of Observations	
Number of Observations Read	20
Number of Observations Used	20
Number of Observations Not Used	0

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=AUCinf (h*ng/mL)

Iteration History				
Iteration Evaluations		-2 Res	Log Like	Criterion
0	1	14.16675553		
1	1	11.37939708	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.05140
Residual	0.04819

Fit Statistics	
-2 Res Log Likelihood	11.4
AIC (Smaller is Better)	15.4
AICC (Smaller is Better)	16.2
BIC (Smaller is Better)	16.0

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=AUCinf (h*ng/mL)

Type 3 Tests of Fixed
Effects

NumDen			
Effect	DF	DF F	ValuePr > F
TRTP	1	9	0.350.5704

Coefficients for DC-806 + Digoxin + Rosuvastatin vs
Digoxin + Rosuvastatin

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Digoxin + Rosuvastatin	1
TRTP	Digoxin + Rosuvastatin	-1

Estimates

Label	Standard			
	Estimate	ErrorDFt	ValuePr > t Alpha	Lower Upper
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	-0.05782	0.09818	9	-0.59 0.5704 0.1-0.23780.1221

Least Squares Means

Standard				
EffectPlanned Treatment	Estimate	ErrorDf	t ValuePr > t Alpha Lower Upper	
TRTP DC-806 + Digoxin + Rosuvastatin	3.1389	0.09980	9 31.45 <.0001	0.12.95603.3219
TRTP Digoxin + Rosuvastatin	3.1967	0.09980	9 32.03 <.0001	0.13.01383.3797

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure
Parameter Category 1=Rosuvastatin Parameter=AUClast (h*ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues	
TRTP	2DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin
SUBJID	CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	I
Max Obs per Subject	24

Number of Observations	
Number of Observations Read	24
Number of Observations Used	24
Number of Observations Not Used	0

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=AUClast (h*ng/mL)

Iteration History				
Iteration Evaluations -2 Res Log Like Criterion				
0	1	35.88614850		
1	1	26.91845933	0.00000000	

Convergence criteria met.

Covariance Parameter Estimates	
Cov Parm Estimate	
SUBJID	0.1782
Residual	0.06047

Fit Statistics	
-2 Res Log Likelihood	26.9
AIC (Smaller is Better)	30.9
AICC (Smaller is Better)	31.6
BIC (Smaller is Better)	31.9

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=AUClast (h*ng/mL)

Type 3 Tests of Fixed
Effects

		NumDen
Effect	DF	ValuePr > F
TRTP	1 11	1.940.1909

Coefficients for DC-806 + Digoxin + Rosuvastatin vs
Digoxin + Rosuvastatin

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Digoxin + Rosuvastatin	1
TRTP	Digoxin + Rosuvastatin	-1

Estimates

Label	Standard		ErrorDFt	ValuePr > t	Alpha	Lower	Upper
	Estimate						
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	-0.1399	0.100411	-1.39	0.1909	0.1	-0.32020	0.04036

Least Squares Means

		Standard		ErrorDFt	ValuePr > t	Alpha	Lower	Upper
Effect	Planned Treatment	Estimate						
TRTP	DC-806 + Digoxin + Rosuvastatin	3.1911	0.141011	22.63	<.0001	0.1	2.93783	3.4444
TRTP	Digoxin + Rosuvastatin	3.3310	0.141011	23.62	<.0001	0.1	3.07773	3.5843

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=Cmax (ng/mL)

Model Information	
Data Set	WORK.PK2
Dependent Variable	LNAVAL
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class LevelsValues

TRTP 2DC-806 + Digoxin + Rosuvastatin Digoxin + Rosuvastatin

SUBJID

CCI

Dimensions	
Covariance Parameters	2
Columns in X	3
Columns in Z	CCI
Subjects	1
Max Obs per Subject	26

Number of Observations	
Number of Observations Read	26
Number of Observations Used	26
Number of Observations Not Used	0

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=Cmax (ng/mL)

Iteration History				
Iteration	Evaluations	-2 Res	Log Like	Criterion
0	1	1	51.45208238	
1	1	1	48.58664179	0.00000000

Convergence criteria met.

Covariance
Parameter
Estimates

Cov Parm Estimate	
SUBJID	0.1859
Residual	0.2175

Fit Statistics

-2 Res Log Likelihood	48.6
AIC (Smaller is Better)	52.6
AICC (Smaller is Better)	53.2
BIC (Smaller is Better)	53.7

Appendix 16.1.9.2.3
Statistical Methods and Analysis Output
Supporting Table 14.2.3.2.b

The Mixed Procedure

Parameter Category 1=Rosuvastatin Parameter=Cmax (ng/mL)

Type 3 Tests of Fixed Effects

		NumDen
Effect	DF	ValuePr > F
TRTP	1 12	0.290.5982

Coefficients for DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin

Effect	Planned Treatment	Row1
Intercept		
TRTP	DC-806 + Digoxin + Rosuvastatin	1
TRTP	Digoxin + Rosuvastatin	-1

Estimates

Label	Standard		Standard	
	Estimate	ErrorDFt	ValuePr > t Alpha	Lower Upper
DC-806 + Digoxin + Rosuvastatin vs Digoxin + Rosuvastatin	-0.09902	0.182912	-0.54 0.5982	0.1 -0.4250 0.2270

Least Squares Means

		Standard	
Effect	Planned Treatment	Estimate	ErrorDFt ValuePr > t Alpha Lower Upper
TRTP	DC-806 + Digoxin + Rosuvastatin	0.9648	0.176212 5.48 0.0001 0.10.65091.2788
TRTP	Digoxin + Rosuvastatin	1.0638	0.176212 6.04 <.0001 0.10.74991.3778