Protocol J5B-MC-FHAE V2

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: 27-Sep-2023

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

CONFIDENTIAL

Sponsor code: DCE806104

ICON code: DITBEE43-0D1NX8

IND number: 163686

A drug-drug interaction study evaluating the perpetrator potential of DC-806 on cocktails of CYP450 enzyme and transporter substrates in healthy participants

Investigational product:	DC-806
Clinical phase:	Phase 1 study
Indication to be studied:	Not applicable
Sponsor:	DICE Therapeutics, Inc. A wholly owned subsidiary of Eli Lilly and Company 400 East Jamie Court, Suite 300 South San Francisco, CA 94080 US
Contract Research Organization:	ICON Early Clinical Development Services 1255 East 3900 South Salt Lake City, UT 84124 US
Principal Investigator:	PPD Research Physician - Early Phase Clinical Services Tel: PPD E-mail: PPD

Version 2.0, 27-Sep-2023

This study will be performed in compliance with the principles of Good Clinical Practice.

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SPONSOR AUTHORIZATION OF CLINICAL STUDY PROTOCOL

The Sponsor and the Contract Research Organization agree to conduct the study as outlined in this clinical study protocol. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Contract Research Organization and must be documented in writing.

Name/Position: Date: Signature:

Sponsor
DICE Therapeutics, Inc.
A wholly owned subsidiary of Eli Lilly and Company
400 East Jamie Court, Suite 300
South San Francisco, CA 94080

Sponsor's Contact
PPD
Vice President, Development Sciences
DICE Therapeutics, Inc.
Tel: PPD
E-mail: PPD

Sponsor Signatory
PPD
VP, Clinical Development

PPD PPD
27 Sep 2023 16:19:11 UTC (Z)
REASON: I approve this document
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AUTHORIZATION OF CLINICAL STUDY PROTOCOL BY CONTRACT RESEARCH ORGANIZATION

The Sponsor and the Contract Research Organization agree to conduct the study as outlined in this clinical study protocol. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Contract Research Organization and must be documented in writing.

Name/Position: Date: Signature:

Contract Research Organization:
ICON Early Clinical Development Services
1255 East 3900 South
Salt Lake City, UT 84124 US

Principal Investigator
PPD
Research Physician - Early Phase Clinical Services

PPD PPD
27 Sep 2023 17:09:38 UTC (Z)
REASON: I approve this document
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SERIOUS ADVERSE EVENT CONTACT INFORMATION

In case of a serious adverse event (SAE; see Appendix 8.2), the Principal Investigator will send a report within 24 hours of notification to Drug Safety (according to the contact information included in the investigator site file).

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SUMMARY OF CHANGES

The following changes have been introduced in Version 2.0 of the protocol (dated 21 Sep 2023).

Document	Date of Issue	Summary of Changes
Version 2.0	27 Sep 2023	The following changes were made: Synopsis, Schedule of Assessments (SOAs): - The SOA in Table 1, Cohort 1 has been corrected to show that the X was removed from the clinical laboratory row for Day 7 and X added to Day 8 to align with the corresponding footnote d which has been updated. Per footnote d: 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. Timing of clinical laboratory assessments have been updated to align with DC-806 and probe substrate dosing. - The SOA in Table 2, Cohort 2 has been corrected to show that the X was removed from the clinical laboratory row for Day 8 and X added to Days 5 and 10 to align with the corresponding footnote d which has been updated. Per footnote d: 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. Timing of clinical laboratory assessments have been updated to align with DC-806 and probe substrate dosing. - The SOA in Table 2, Cohort 2 has been corrected to reflect that Xs were removed from the digoxin/rosuvastatin probe substrate cocktail dosing row for Day 2 and Day 9 to align with the study design. - The SOA in Table 2, Cohort 2 has been corrected to reflect that Xs have been added to the vital signs row for Day 2 and Day 9 to align with the corresponding footnote g. Per footnote g: vital signs taken at 24 hours after Day 1 probe substrate cocktail dosing and 24 hours after Day 8 probe substrate cocktail dosing. - The SOA in Table 1 (Cohort 1) and Table 2 (Cohort 2) have been updated to show that the row “DC-806 Dosing” has been changed to “DC-806 BID Dosing”, to clarify that there will be two doses of DC-806 on each designated dosing day. Synopsis, Schedule of Sampling for PK Assessments for Probe Substrates: - Table 3, Cohort 1. The following footnote was added: “The exception is the Day 7 predose PK sample for the probe substrate which will have a sampling window within 120 minutes of dosing to allow it to coincide with the Day 7 predose PK sample collection for DC-806”. The sampling window was extended to decrease the number of blood collections/draws for the participants where feasible. - Table 5, Cohort 2. The following footnote was added: “The exception is the Day 8 predose PK sample for the probe

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		substrate which will have a sampling window within 120 minutes of dosing to allow it to coincide with the Day 8 predose PK sample collection for DC-806". The sampling window was extended to decrease the number of blood collections/draws for the participants where feasible. Section 3.5.1.2.2 – Clinical Laboratory Assessments: - Fasting glucose will be measured for both cohorts 1 and 2 as part of clinical chemistry, however only cohort 1 will have additional blood glucose monitoring using a glucometer at designated timepoints post repaglinide dosing due to potential effect of repaglinide on glycemic control. Section 3.5.1.2.3 - Vital Signs: - Added text to clarify that pulse oximetry measurement is for Cohort 1 only. Section 3.5.1.4 - Total of Blood Volume: - Increased total blood volume from 500 mL to 525 mL to provide necessary plasma volume for the bioanalytical assays.
Original Protocol (Version 1.0)	30 Aug 2023	Not Applicable

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SYNOPSIS

Study 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

Short Study Title

A drug-drug interaction study evaluating the perpetrator potential of DC-806 on cocktails of CYP450 enzyme or transporter substrates in healthy participants

Study Codes

Sponsor code:	DCE806104
ICON code:	DITBEE43-0D1NX8
IND number:	163686

Sponsor

DICE Therapeutics, Inc.
A wholly owned subsidiary of Eli Lilly and Company
400 East Jamie Court, Suite 300
South San Francisco, CA 94080

Sponsor's Contact

PPD
VP, Development Sciences
DICE Therapeutics, Inc.
Tel: PPD
email: PPD

Contract Research Organization

ICON – Early Development Services (EDS)
9755 Ridge Drive
Lenexa, KS 66219

Principal Investigator

PPD
Research Physician, Early Phase Clinical Services
Tel:PPD
E-mail: PPD

Medical Monitor

PPD
Medical Director, Early Phase Clinical Services
Tel: PPD
E-mail: PPD

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Objectives and Endpoints

Objectives	Endpoints
Primary	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	• 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}
Secondary	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	• Incidence of AEs • Change from baseline in clinical laboratory values, vital signs, 12-lead ECGs and physical examination findings
Exploratory	Exploratory
CCI	

AE=adverse event; BCRP=breast cancer resistant protein; CYP=cytochrome P450; ECG=electrocardiogram; OATP=organic anion transporter protein; P-gp=permeability glycoprotein; PK=pharmacokinetic(s)

Design and Treatments

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 (n = CCI) — Probe substrate cocktail includes midazolam (CYP3A4 substrate) and repaglinide (CYP2C8 substrate)

Period 1: A single oral dose of the 2-probe substrate cocktail consisting of CCI mg midazolam and CCI mg repaglinide administered under fasted conditions in the morning on Day 1

Period 2: Twice-daily oral doses of CCI mg DC-806 administered 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 in the morning of Day 7 under fasted conditions, 1.5 hours (±15 min) after DC-806 dosing, while DC-806 BID dosing will be continued until the end of Day 8 (final dose given in the evening of Day 8)

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Cohort 2 (n = CCI	Probe substrate cocktail includes digoxin (P-gp substrate) and rosuvastatin (BCRP/OATP1B1 substrate)
Period 1:	A single oral dose of the 2-probe substrate cocktail consisting of CCI mg digoxin and CCI mg rosuvastatin administered under fasted conditions in the morning on Day 1
Period 2:	Twice-daily oral doses of CCI mg DC-806 administered 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 in the morning of Day 8 under fasted conditions, 1.5 hour (±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)

For each participant, the study will consist of an eligibility screening period of up to 28 days.
During the treatment periods, safety and PK assessments will be performed with PK blood sampling for up to 48 hours (Cohort 1) and up to 96 hours (Cohort 2) after administration of each 2-probe substrate cocktail.
Participants will be discharged after the last PK sample collection in Period 2 in the morning of Day 9 (Cohort 1), or Day 12 (Cohort 2).
A follow-up visit will be performed 5 (±2) days after collection of the last PK blood sample on Day 9 (Cohort 1), 8 (±2) days after collection of the last PK blood sample on Day 12 (Cohort 2), or at the time of early termination (ET).

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:	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:	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 hr) 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:	5 (±2) days after collection of the last PK blood sample on Day 9 (Cohort 1), 8 (±2) days after collection of the last PK blood sample on Day 12 (Cohort 2), or at the time of ET.

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Participants

Up to 28 healthy male and female participants will be enrolled to have approximately CCI evaluable participants in each cohort. Early termination participants may be replaced upon mutual agreement between the Sponsor and ICON for this study.

Main Criteria for Inclusion

Sex:	Male or female; females must be of nonchildbearing potential, or postmenopausal
Age:	18 years to 55 years, inclusive, at screening
Weight:	≥50 kg, at screening
Body Mass Index:	18.0 kg/m^2 to 32.0 kg/m^2, inclusive, at screening
Status:	Healthy participants

Study Drug

Active Investigational Medicine

Active substance	DC-806
Activity	CCI
Strength	CCI mg
Dosage form	Oral CCI
Manufacturer	Patheon Pharmaceuticals Inc. (Thermo Fisher Scientific Inc.)

Probe Substrate

Active substance	Midazolam
Activity	Short-acting benzodiazepine CNS depressant, used as CYP3A4 probe substrate
Strength	CCI mg/mL
Dosage form	Oral Syrup
Manufacturer	Sourced by pharmacy at ICON

Probe Substrate

Active substance	Repaglinide
Activity	Insulin secretagogue, used as CYP2C8 probe substrate
Strength	CCI mg
Dosage form	Oral Tablet
Manufacturer	Sourced by pharmacy at ICON

Probe Substrate

Active substance	Digoxin
Activity	Cardiac Glycoside, inhibits sodium-potassium ATPase of the myocyte, used as P-gp probe substrate
Strength	CCI mg
Dosage form	Oral Tablet
Manufacturer	Sourced by pharmacy at ICON

Probe Substrate

Active substance	Rosuvastatin
Activity	HMGCoA reductase inhibitor, used as BCRP/OATP1B1 probe substrate

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Strength	CCI mg
Dosage form	Oral Tablet
Manufacturer	Sourced by pharmacy at ICON

Assessments

Safety	Adverse events (AEs), clinical laboratory, vital signs, 12-lead electrocardiograms (ECGs), physical examinations.
Pharmacokinetics	Plasma concentrations of probe cocktail substrates after single dose. Plasma concentrations of DC-806 after multiple dosing (steady state). Primary PK parameters (C_{max}, AUC_{0-t}, AUC_{0-inf}) of midazolam and 1--hydroxymidazolam, repaglinide, digoxin, rosuvastatin. Exploratory CCI [redacted]

Statistical Methods

Sample size calculation	The sample size is not based on statistical considerations but is consistent with similar reported studies and considered sufficient to achieve the study objectives.
Safety	Listings, tables, and descriptive statistics as described in the statistical analysis plan (SAP).
Pharmacokinetics	Plasma PK parameters (for the 4 probe substrates evaluated) calculated using noncompartmental analysis, including but not limited to C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf}, CL/F, V_z/F, as appropriate. Listings and tables with the following descriptive statistics for probe substrate and DC-806 plasma concentrations and plasma PK parameters: n, mean, standard deviation (SD), coefficient of variation (CV), minimum, median, maximum, geometric mean, CV of geometric mean. Linear (±SD) and semi-logarithmic (+SD) plots of the arithmetic mean plasma concentrations versus time will be provided for each substrate (and relevant metabolite) to visually assess the impact of DC-806 on PK of evaluated substrates. The effect of DC-806 on the PK of each of the probe substrates midazolam (and its active metabolite, 1-hydroxymidazolam), repaglinide, digoxin and rosuvastatin will be analyzed separately. The geometric mean ratio and associated CCI % CI of each probe substrate coadministered with DC-806 compared with the probe substrate alone will be calculated for C_{max}, AUC_{0-t}, and AUC_{0-inf}. These values will be estimated from a linear mixed-effects model on the natural log-transformed value of the parameter including a fixed effect for treatment and a random subject-level effect and presented along with the model estimates of least-squares geometric mean values in each treatment period.

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Exploratory	CCI [redacted] will be reported by the descriptive statistics. CCI [redacted]

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Table 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											

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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
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 Post Repaglinide Dosing [e]				X						X			
12-Lead ECG [f, g]	X		X						X	X			X
Vital Signs [h]	X		X	X	X					X	X		X
Continuous Pulse Oximetry Post Midazolam Dosing [i]				X						X			
Eligibility Check	X	X	X										
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 Table 3 and Table 4										
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X

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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
AE Monitoring [m, n]	X	X	X	X[o]	X	X	X	X	X	X[o]	X	X	X

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

a. Confinement on Day -1.
b. Participants will be discharged from the clinical site on Day 9 after the last PK sampling.
c. 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.
d. 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.
e. Blood glucose test every 30 minutes from 0.5 hours to 4 hours post repaglinide dose on Day 1 and Day 7.
f. 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.
g. 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.
h. 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.
i. Continuous measuring of pulse oximetry and respiratory rate through 6 hours post midazolam dosing on Day 1 and Day 7.
j. 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.
k. 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.
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).

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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.

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Table 2 Schedule of Assessments – Cohort 2

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	10	11	12	8 (±2) days after collection of the last PK blood sample on Day 12 or time of ET
Confinement		X[a]	X	X	X	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															
Drug and Alcohol Screen	X	X														

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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**	**10**	**11**	**12**	8 (±2) days after collection of the last PK blood sample on Day 12 or time of ET
Pregnancy Test (for all females)	X	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				X
Eligibility Check	X	X	X													
Digoxin/Rosuva-statin Probe Substrate Cocktail Dosing [h]				X							X					
DC-806 BID Dosing [i]								X	X	X	X	X				
Blood Sampling for PK [j]			See Table 5 and Table 6													
Previous and Concomitant Medication	X	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	X

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)

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a. Confinement on Day -1.
b. Participants will be discharged from the clinic site on Day 12 after the last PK sampling.
c. 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.
d. 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.
e. 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.
f. 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.
g. 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.
h. 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.
i. 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.
j. Please refer to Tables 5 and 6 for details.
k. 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.

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Table 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	24	48
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. The exception is the Day 7 predose PK sample for the probe substrate which will have a sampling window within 120 minutes of dosing to allow it to coincide with the Day 7 predose PK sample collection for DC-806.

Table 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
Nominal Timepoint (hours) for DC-806	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.

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Table 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	24	48	72	96
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. The exception is the Day 8 predose PK sample for the probe substrate which will have a sampling window within 120 minutes of dosing to allow it to coincide with the Day 8 predose PK sample collection for DC-806.

Table 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 (-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.

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistant protein
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CK	creatine kinase
CHMP	Committee for Medicinal Products for Human Use
CSP	clinical study protocol
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	intravenous
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
OATP	organic anion transporter protein
P-gp	Permeability glycoprotein
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
WMA	World Medical Association

Note: Definitions of pharmacokinetic (PK) parameters are provided in Section 3.6.2.

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1. INTRODUCTION

1.1 Background

1.1.1 DC-806

Psoriasis is a chronic, relapsing inflammatory disease of the skin with a reported prevalence range across countries of 0.09% to 11.4% affecting approximately 1% to 3% of the world's population. While psoriasis can manifest at any age, there is a bimodal age distribution during the second to fourth and sixth to seventh decades of life. The most common form is plaque psoriasis representing 80% to 90% of all cases. Plaque psoriasis is defined by well-defined/demarcated red, scaly plaques, or patches. It can occur anywhere on the body but most commonly affects extensor surfaces such as elbows and knees, gluteal folds, scalp, and trunk.[1]

While the etiology of psoriasis is unknown, genetic susceptibility and environmental triggers may play key roles in the aberrant immune response resulting in disordered keratinocyte differentiation, proliferation, and inflammation. CCI [redacted]

DC-806 is an orally administered, small-molecule inhibitor of the CCI [redacted]. DC-806 specifically binds to CCI [redacted] and prevents the CCI [redacted] and CCI [redacted] from binding to the CCI [redacted]. DC-806 is being developed as an oral therapy for psoriasis. In a rat model of rheumatoid arthritis mediated by CCI [redacted], DC-806 ameliorated disease to a similar degree as CCI [redacted].

Details on the mechanism of action of DC-806 and nonclinical data are provided in the DC-806 investigator's brochure (IB).[1]

1.1.2 Clinical Safety Data

One clinical study of DC-806 has been completed. Study DCE806101 was a Phase 1, randomized, double-blind, placebo-controlled, 3-part study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single-ascending and multiple-ascending doses of DC-806 in healthy adult participants and multiple-ascending doses of DC-806 in participants with mild to moderate plaque psoriasis.

In Part 1 (single-ascending doses in healthy participants), a total of 30 participants received single doses of DC-806 (25 mg to 800 mg) and 10 participants received placebo. In Part 2 (multiple-ascending doses in healthy participants), a total of 24 participants received multiple doses of DC-806 (175 mg once daily [QD]; or 200 mg, 400 mg, or 800 mg twice daily [BID]) and 8 participants received placebo for 7 days. In Part 3 (multiple-ascending doses in participants with psoriasis), 13 participants received 200 mg BID DC-806, 8 received 800 mg BID DC-806, and 11 received placebo BID for up to 28 days.

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Doses of DC-806 up to 800 mg BID were generally well tolerated following single- and multiple-ascending dose administration in adult healthy participants and after BID doses for up to 28 days in participants with psoriasis. There were no treatment-related discontinuations due to treatment-emergent adverse events (TEAEs), severe adverse events (SAEs), and no clinically significant abnormalities in laboratory parameters, physical examination, vital signs, or electrocardiograms (ECGs). All TEAEs were mild to moderate in severity, with only 3 TEAEs considered as treatment-related (mild nausea with onset on Day 2 in a healthy participant in the 800 mg BID DC-806 group and mild abdominal discomfort and mild nausea with onset on Day 1 in a participant with psoriasis in the 800 mg BID group). There were no dose-dependent trends in the number, severity, or types of TEAEs.

The most common TEAEs reported following single-dose administration of DC-806 in healthy participants were headache and medical device site reaction (rash due to Holter electrode placement). The most common TEAEs reported following multiple-dose administration in healthy participants were headache and nausea in the overall DC-806 group, and medical device site reaction (rash secondary to Holter/ECG electrode placement) in the placebo group. In participants with psoriasis, the most common TEAEs were headache, coronavirus disease 2019 (COVID-19) infection, abdominal discomfort, and skin abrasion in the DC-806 treatment groups, and tonsillitis in the placebo group.

In an exploratory analysis of the clinical activity of DC-806 in participants with mild to moderate plaque psoriasis, significant improvement in Psoriasis Area Severity Index score was observed after treatment with DC-806 800 mg BID for 28 days compared to placebo. More details of Study DCE806101 are provided in the DC-806 IB.[1]

Midazolam (used as a CYP3A4 substrate), repaglinide (used as a CYP2C8 substrate), digoxin (used as a P-gp transporter substrate) and rosuvastatin (used as a BCRP/OATP1B1 transporter substrate) are registered drugs, and at the proposed doses the safety and tolerability for these drugs are well characterized.[2, 3, 4, 5]

1.1.3 Clinical Pharmacokinetics of Study Drugs

DC-806

The Phase 1 study DCE806101 evaluated the PK of DC-806 following single-ascending and multiple-ascending dose administration in adult healthy participants and multiple-dose administration in participants with psoriasis.

Following administration of single-ascending doses of DC-806 up to 800 mg in healthy participants, DC-806 absorption was rapid with median time to peak concentration (t_{max}) ranging from 0.75 to 1.75 hours postdose. DC-806 exposure increased with increasing DC-806 doses, with the highest peak concentration (C_{max}) and area under the concentration-time curve (AUC) values observed in the 800 mg dose group (C_{max}=2783 ng/mL and $AUC_{0-\infty}$=8415 ng·h/mL). The average elimination half-life ranged from 2.2 to 9.8 hours. Minimal food effect (19% lower C_{max} and 12% lower AUC) was observed after administration of 200 mg DC-806 with a high-fat, high-calorie meal as compared to dosing under fasting conditions.

Following administration of multiple-ascending doses of DC-806 up to 800 mg BID in healthy participants for 7 days, DC-806 absorption was rapid with median t_{max} ranging from 0.5 to 1.25 hours postdose on Day 7. Steady state was reached within 3 days of BID dosing. DC-806 exposure

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increased with increasing DC-806 doses in a slightly higher than dose-proportional manner (log/log dose linearity slope >1, but <1.5 on average), with highest C_{max} and AUC values observed in the 800 mg BID dose group (average steady state C_{max}=3958 ng/mL and AUC_{0-12}=9372 ng·h/mL). The average elimination half-life ranged from 11.3 to 12.2 hours after reaching steady state for BID regimens. Moderate intrasubject variability in exposure was observed, with the coefficient of variation for C_{max} and AUC ranging between 23% and 45%. The fraction of unchanged DC-806 excreted in the urine was relatively small, ranging from 1.2% to 3.4% of the administered dose. Renal clearance values were consistently low (2.43 L/h and 2.87 L/h at steady state) compared to apparent plasma clearance of 134.8 L/h and 89.0 L/h in the 400 mg BID and 800 mg BID groups.

Exposure of DC-806 in participants with mild to moderate psoriasis was similar to that observed in healthy participants, when comparing C_{trough} and C_{max} values.

Details of the clinical PK/PD, and preliminary clinical activities of DC-806 are provided in the DC806 IB.[1]

Midazolam

Absorption: Midazolam is rapidly absorbed after oral administration and is subject to substantial intestinal and hepatic first-pass metabolism. The PK of midazolam and its major metabolite, 1-hydroxymidazolam, and the absolute bioavailability of midazolam HCl syrup were studied in pediatric patients of different ages (6 months to <16 years old) over a 0.25 to 1.0 mg/kg dose range. The mean T_{max} values across dose groups (0.25, 0.5, and 1.0 mg/kg) range from 0.17 to 2.65 hours. Midazolam exhibits linear pharmacokinetics between oral doses of 0.25 to 1.0 mg/kg (up to a maximum dose of 40 mg) across the age groups ranging from 6 months to <16 years. The absolute bioavailability of the midazolam HCl syrup in pediatric patients is about 36%, which is not affected by pediatric age or weight. The $AUC_{0-\infty}$ ratio of 1-hydroxymidazolam to midazolam for the oral dose in pediatric patients is higher than for an intravenous (IV) dose (0.38 to 0.75 versus 0.21 to 0.39 across the age group of 6 months to <16 years), and the $AUC_{0-\infty}$ ratio of 1-hydroxymidazolam to midazolam for the oral dose is slightly higher in pediatric patients than in adults (0.38 to 0.75 versus 0.40 to 0.56).[2]

Distribution: The extent of plasma protein binding of midazolam is moderately high and concentration independent. In adults and pediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin. In healthy volunteers, 1-hydroxymidazolam is bound to the extent of 89%.[2]

Elimination: The mean elimination half-life of midazolam is about 2.3 hours following single oral doses of midazolam HCl syrup.[2]

Metabolism: Midazolam is primarily metabolized in the liver and gut by human CYP3A4 to its pharmacologic active metabolite, 1-hydroxymidazolam, followed by glucuronidation of the 1-hydroxyl metabolite which is present in unconjugated and conjugated forms in human plasma. The 1-hydroxymidazolam glucuronide is then excreted in urine. In tracing tests, 1-hydroxymidazolam is equipotent and equally effective as unchanged midazolam on a total plasma concentration basis. After oral or IV administration, 63% to 80% of midazolam is recovered in urine as 1-hydroxymidazolam glucuronide. No significant amount of parent drug or metabolites is extractable from urine before beta-glucuronidase and sulfatase deconjugation, indicating that the urinary metabolites are excreted mainly as conjugates. Midazolam is also metabolized to two other minor

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metabolites: 4-hydroxy metabolite (about 3% of the dose) and 1,4-dihydroxy metabolite (about 1% of the dose) are excreted in small amounts in the urine as conjugates.[2]

Repaglinide

Absorption: After oral administration, repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels occur within 1 hour. The mean absolute bioavailability is 56%.[3]

Distribution: After IV dosing in healthy subjects, the volume of distribution at steady state (V_{ss}) was 31 L. Protein binding and binding to human serum albumin was greater than 98%.[3]

Elimination: Repaglinide is rapidly eliminated from the plasma with a half-life of approximately 1 hour. The total body clearance (CL) after IV dosing in healthy subjects was 38 L/h. Within 96 hours after dosing with C^{14}-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.[3]

Metabolism: Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of repaglinide.[3]

Digoxin

Absorption: Following oral administration, peak plasma concentrations of digoxin occur at 1 to 3 hours. Absorption of digoxin from lanoxin tablets has been demonstrated to be 60-80% complete compared to an identical intravenous dose of digoxin (absolute bioavailability). Digoxin is a substrate for P-gp. As an efflux protein on the apical membrane of enterocytes, P-gp may limit the absorption of digoxin.[4]

Distribution: Following oral administration, a 6-8 hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution (approximately 475-500 L). Digoxin crosses both the blood-brain barrier and the placenta. Approximately 25% of digoxin in the plasma is bound to protein.[4]

Elimination: Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to healthy volunteers, 50-70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to creatinine clearance and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5-2 days.[4]

Metabolism: Only a small percentage (13%) of a dose of digoxin is metabolized in healthy volunteers. The urinary metabolites, which include dihydrodigoxin, digoxigenin bisdigitoxoside, and their glucuronide and sulfate conjugates are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the

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cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.[4]

Rosuvastatin

Absorption: After oral administration, peak plasma concentrations of rosuvastatin are reached in 3 to 5 hours. Both C_{max} and AUC increased in approximate proportion to dose. The absolute bioavailability of rosuvastatin is approximately 20%. The AUC of rosuvastatin does not differ following evening or morning drug administration.[5]

Distribution: Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.[5]

Elimination: Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route. The elimination half-life of rosuvastatin is approximately 19 hours.[5]

Metabolism: Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 \ 2C9, and in vitro studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.[5]

1.2 Risk-benefit Assessment and Risk Mitigation

There is no expected clinical benefit (beyond that of an assessment of their medical status) for the healthy participants in this study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. The information obtained in this study can be used for the further clinical development of DC-806. More detailed information about the known and expected benefits, risks, and reasonably expected AEs of DC-806 can be found in the IB.[1]

DC-806 at doses up to CCI mg BID was generally well tolerated following single and multiple -ascending dose administration in adult healthy participants and participants with psoriasis.

Based on in vitro experimental assessments, a moderate effect of DC-806 on the exposures of the CYP probe substrates midazolam and repaglinide or transporter substrates digoxin and rosuvastatin of up to CCI is predicted. However, twice daily dosing of an CCI mg dose of DC-806 for 5 days in each cohort is not expected to result in unacceptable AEs in healthy participants given that substrates to be evaluated in this study are not anticipated to impact the PK of DC-806, and DC-806 dosing is at a short duration (5 days) compared to the completed phase I study where the CCI mg BID dose administered out to 28 days was well tolerated.

Based on the available nonclinical and clinical data, the safety profile of DC-806 is considered adequate for the proposed clinical study in healthy adult participants. In addition, the inclusion and exclusion criteria and safety monitoring employed in this protocol are anticipated to be able to protect the participants' safety and detect TEAEs.

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CCI have been associated with the risk of serious infections and opportunistic infections. To minimize such potential risks observed with other CCI, participants with the following medical conditions will be excluded: significant and/or acute illness within 5 days prior to study drug administration that may impact safety assessments and infections including human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus (HCV).

Safety in this study will be assessed through the medical review of adverse events (AEs), vital signs, 12-lead ECGs, clinical laboratory data (hematology, clinical chemistry, and urinalysis), and physical examination findings. Nonclinical data have identified minimal magnitude increases in heart rate-corrected QT interval at high doses in the 28-day and 13-week general toxicity studies in dogs. However, these increases were neither observed in the definitive nonclinical cardiovascular study nor in the completed phase I clinical study; nevertheless, ECGs will be monitored during the study.

DC-806 at doses up to CCI mg BID was generally well tolerated following single and multiple ascending dose administration in healthy adult participants. Nevertheless, participants will be carefully monitored after dosing.

Midazolam, repaglinide, digoxin and rosuvastatin are registered drugs, and at the proposed doses the safety and tolerability for these drugs are well known. See the full prescribing information for a detailed list of adverse reactions reported.[2, 3, 4, 5] The use of these agents in this study is consistent with best practices for evaluating drug-drug interaction (DDIs).

Midazolam: Midazolam is a member of a class of medicines called benzodiazepines and is generally used for sedation and relief of anxiety prior to diagnostic, surgical, therapeutic or endoscopic procedures and as a premedication for general anesthesia. Midazolam causes sleepiness, and may also cause agitation, involuntary movements, hyperactivity, and serious respiratory problems. Midazolam has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings, and should be used only in hospital or ambulatory care settings that have the personnel and equipment for monitoring and resuscitation.

Repaglinide: Repaglinide is an oral antidiabetic medicine which lowers blood glucose. Other side effects include stomach pain and diarrhea; severe liver problems, abnormal liver function, and increase in liver enzymes have very rarely been reported.

Digoxin: Digoxin is used to treat arrhythmias such as atrial fibrillation and atrial flutter, and heart failure. Digoxin works by slowing down the heart rate. Digoxin may cause cardiac arrhythmias, dizziness, blurred vision, nausea, vomiting, diarrhea, and skin rash.

Rosuvastatin: Rosuvastatin belongs to a group of medicines called statins which are used to reduce low density lipoprotein (LDL) cholesterol, and reduce the risk of stroke or myocardial infarction. Rosuvastatin may cause myopathy or rhabdomyolysis, hepatic dysfunction, proteinuria, hematuria, increases in HbA1c and fasting serum glucose levels, and rarely immune-mediated necrotizing myopathy.

The use of cocktail probes has been validated in several clinical studies[6, 7, 8, 12] and the FDA also recommends the use of cocktails of substrates.[9] The selected doses for midazolam, repaglinide, digoxin and rosuvastatin have accounted for the potential for moderate increases in exposure by DC-806. The increased exposure at these selected doses of substrates due to the impact of CYP/transporter inhibitors has been evaluated and were shown to be well tolerated in healthy

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participants in several DDI studies using the same dose levels selected for these substrates in this study.[6, 7, 8,11, 12]

Overall, on the basis of the available nonclinical and clinical data, and prior knowledge, the risk-benefit profile of DC-806 is judged by the Sponsor as acceptable for the proposed clinical study.

1.3 Study Rationale

In view of the available nonclinical and clinical data, further development of DC-806 for the treatment of psoriasis is warranted. DDI studies have an important role in drug development, with objectives being to determine whether there is a potential for a drug interaction between an investigational drug and other drugs that may be coadministered in patients.[9]

In an in vitro DDI risk assessment for DC-806, the potential for DC-806 to inhibit the major CYP enzymes in human liver microsomes was evaluated by determining their respective IC_{50} values. Among all CYP isoforms evaluated, the only CYP isoforms inhibited by DC-806 with clinically relevant IC_{50} values were CYP2C8 (IC_{50}=CCI µM), and CYP3A4 (IC_{50}=CCI or CCI µM for different 3A4 substrates). In addition, in vitro assessments of DC-806 were also performed for its potential of inhibiting human transporters, using MDCK-II cells or membrane vesicles expressing human transporters. Among all transporters evaluated, DC-806 did not inhibit OAT1, OAT3, OCT2, BCRP (vesicles) and P-gp (vesicles) at concentrations up to CCI µM. For all other transporters evaluated (OCT1, OATP1B3, MATE1, MATE2, BCRP (MDCK cells), and P-gp (MDCK cells), IC_{50} values ranged from CCI -CCI µM except for OATP1B1 which had a low IC_{50} value of CCI µM (refer to IB for more details). It was confirmed that DC-806 is not a substrate for any of the transporters evaluated under the study conditions (with exception of P-gp). The IC_{50} values for BCRP and P-gp inhibition by DC-806 were CCI µM and CCI µM, respectively. According to the FDA guidance[10], DC-806 has the potential of DDI with BCRP and P-gp substrates in the gut, with a I_{gut}/IC_{50} ratio higher than CCI Based on data from these in vitro assessments, DC-806 had a potential to inhibit the metabolism of CYP3A4 and 2C8 substrates or substrates of BCRP/OATP1B1 and P-gp.

This DDI study is designed to characterize the effect of DC-806 on the PK of CYP substrates midazolam (CYP3A4) and repaglinide (CYP2C8) and transporter substrates digoxin (P-gp) and rosuvastatin (BCRP/OATP1B1) in healthy participants under strictly controlled conditions to generate reliable data for the characterization of possible PK interactions and potential impact on the safety profile of DC-806.

The potential effect of DC-806 as a perpetrator of interactions involving CYP3A4 and CYP2C8 will be assessed using midazolam and repaglinide, respectively, as a cocktail of probe substrates to evaluate DC-806 as an inhibitor of CYP3A4 or CYP2C8. Such a drug cocktail approach in DDI studies has been validated and reported.[7, 8] Both of these drugs are recommended by the FDA to be used as CYP isoform specific substrates in DDI studies.[11]

The potential effect of DC-806 as a perpetrator of interactions involving the transporters P-gp and BCRP/OATP1B1 will also be assessed using digoxin and rosuvastatin, respectively, as a cocktail of probe substrates to evaluate DC-806 as an inhibitor of P-gp or BCRP/OATP1B1. Such a drug cocktail approach in DDI studies has been validated and reported.[12]

The rationale for dose selection and discussion of study design is described in Section 3.4.4.

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2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	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	• 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}
Secondary	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	• Incidence of AEs • Change from baseline in clinical laboratory values, vital signs, 12-lead ECGs and physical examination findings
Exploratory	Exploratory
CCI	

AE=adverse event; BCRP=breast cancer resistant protein; CYP=cytochrome P450; ECG=electrocardiogram; OATP=organic anion transporter protein; P-gp=permeability glycoprotein; PK=pharmacokinetic(s)

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3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Type of Study

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 (±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).

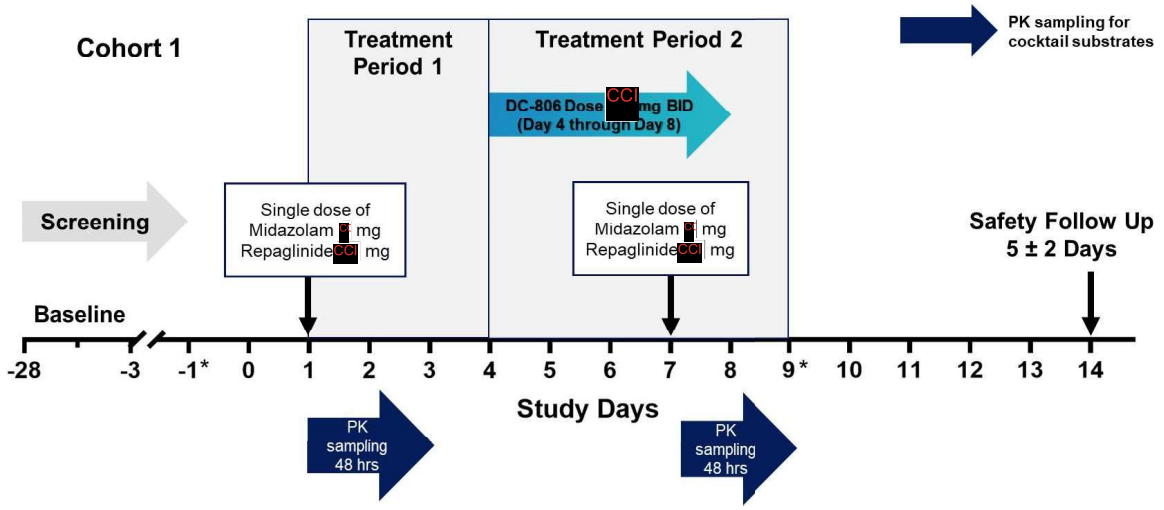
Cohort 2 Study Treatment; digoxin, (P-gp substrate), rosuvastatin (BCRP/OATP1B1 substrate): Each participant will receive a single oral dose of the 2-probe substrate cocktail (CCI mg digoxin and CCI mg rosuvastatin) under fasted conditions in the morning on Day 1 of Period 1. In Period 2, participants 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 (±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.

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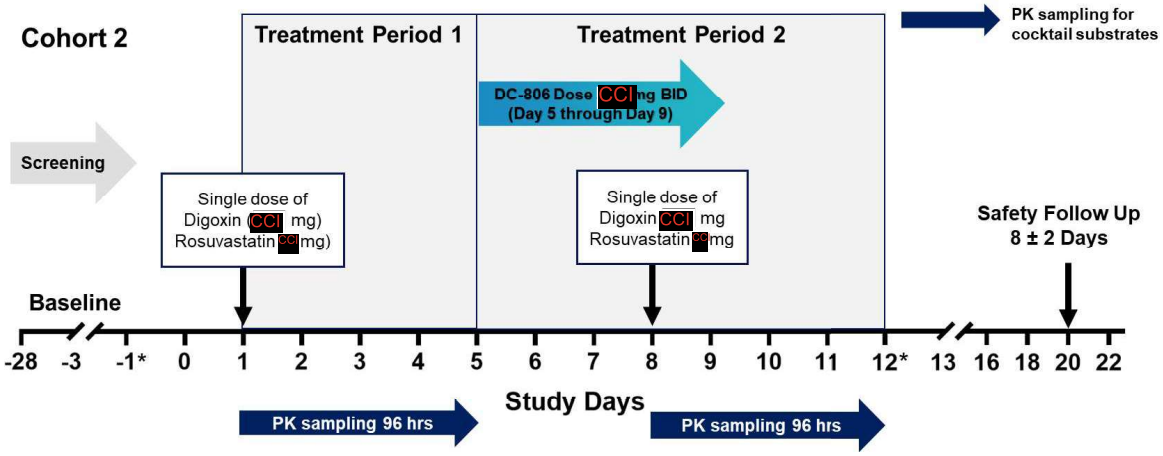
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Figure 1 Study Design Schematic – Cohort 1



*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)

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3.1.2 Screening Period

Participants will report to the clinical site for the eligibility screening (see Section 3.3 for inclusion and exclusion criteria) within 28 days prior to the first study drug administration.

Participants will sign the study-specific informed consent form (ICF) prior to any study -specific screening procedures being performed. The written informed consent will be obtained for all participants, regardless of their eligibility for the study; the signed ICFs will be retained and archived at ICON and a copy will be provided to the participant.

All screening assessments should be conducted within 28 days prior to the first dose of study drug for both cohorts. If any screening assessment falls outside of that window, the Investigator should consult with the ICON's Medical Monitor to determine if the assessment needs to be repeated.

Eligibility screening will consist of the assessments as presented in the schedule(s) of assessments (Table 1 and Table 2).

The treatments planned in this study are described in Section 3.4.1.

3.1.3 Treatment Period

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

Cohort 1

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

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.

Assessments during the treatment period(s) will be performed as presented in the schedule of assessments (Table 1 and Table 2).

3.1.4 Follow-up/Early Termination

The follow-up assessments will be performed 5 (± 2) days after collection of the last PK blood sample on Day 9 (Cohort 1), 8 (±2) days after collection of the last PK blood sample on Day 12 (Cohort 2), or at the time of early termination.

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Assessments during follow-up/early termination will be performed as presented in the schedule of assessments (Table 1 and Table 2).

3.1.5 Start and End of Study and Duration of the Study

The start of the study is defined as the date on which the first participant provides informed consent.

A participant is considered to have completed the study if the participant has completed all study visits.

The end of the study is defined as the date of the last visit or last procedure of the last participant in the study (whichever comes later).

The total duration of the study from screening until follow-up for participants will be 42 (±2) days for Cohort 1 and 48 (±2) days for Cohort 2.

3.2 Discussion of Study Design

3.2.1 Study Population

Healthy participants have been chosen as the study population due to the study design and the low risk of clinically significant toxicity at anticipated exposure levels. Additionally, the duration of exposure is too short to provide clear therapeutic benefit and justify patients discontinuing current therapies. Moreover, use of healthy participants as opposed to patients will allow a clearer interpretation of the PK results, as there will be no confounding factors resulting from changes in disease state and/or concomitant medications.

3.2.2 Type of Study

The fixed-sequence design was chosen to allow each participant to serve as his/her own control and is an acceptable study design for a DDI study. This study will evaluate the effect of DC-806 (CCI mg BID) serving as the perpetrator drug in each cohort on the PK of CYP3A4 probe substrate midazolam and its active metabolite, 1-hydroxymidazolam, CYP2C8 substrate repaglinide (Cohort 1), and P-gp transporter substrate digoxin and BCRP/OATP1B1 transporter substrate rosuvastatin (Cohort 2) in healthy participants.

3.2.2.1 Cohort 1: 2-Probe Cocktail Consisting of Midazolam as a CYP3A4 Substrate, Repaglinide as a CYP2C8 Substrate

Single oral dose of the 2-probe substrate cocktail (CCI mg midazolam and CCI mg repaglinide) will be administered under fasted conditions in the morning on Day 1. DC-806 CCI mg will be dosed twice daily from Day 4 through Day 8 after the washout of the first 2-probe substrate cocktail (midazolam and repaglinide) administration on Day 1. DC-806 dosing starts on Day 4 in Period 2 to ensure that the probe substrate drug levels after the first single dose are mostly (>90%) cleared and that the maximal steady state plasma levels of DC-806 are achieved when a second single dose of the probe substrate cocktail is administered under fasted conditions on Day 7. DC-806 dosing continues until the end of Day 8 so that the PK of the probe substrates can be evaluated while maximal exposure to DC-806 is maintained.

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3.2.2.2 Cohort 2: 2-Probe Cocktail Consisting of Digoxin as a P-gp Substrate and Rosuvastatin as a BCRP/OATP1B1 Substrate

Single oral dose of the 2-probe substrate cocktail (CCI mg digoxin and [redacted] mg rosuvastatin) will be administered under fasted conditions in the morning on Day 1. DC-806, CCI mg will be dosed twice daily from Day 5 through Day 9 after the washout of the first 2-probe substrate cocktail (digoxin and rosuvastatin) administration on Day 1. Dosing of DC-806 starts on Day 5 to ensure that the probe substrate drug levels after the first single dose are mostly cleared (>90%) and that the maximal steady state plasma levels of DC-806 are achieved when a second single dose of the probe substrate cocktail is administered under fasted conditions on Day 8. DC-806 dosing continues until the end of Day 9 so that that the PK of the probe substrates can be evaluated while maximal exposure to DC-806 is maintained.

3.2.3 PK Sampling

Plasma samples will be collected for characterizing the PK of midazolam and its major metabolite 1-hydroxymidazolam, repaglinide and DC-806 (Cohort 1) and PK of digoxin, rosuvastatin and DC-806 (Cohort 2) during the study.

3.2.4 COVID-19 Risk Mitigation

At the discretion of the clinical site, COVID-19 risk mitigation measures may be implemented, if considered to be necessary. This includes, among others, collection of nasal and throat mucosal cell samples and testing these for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using polymerase chain reaction or rapid antigen tests.

Details on specific procedures are described in the site-specific manual and will include all recommendations issued by the US Center for Diseases Control, including specific guidelines related to clinical research executed in clinical research units.

In cases where participants are not able to attend study visits due to an infection with SARS-CoV-2, the Investigator will discuss with the Sponsor potential mitigation approaches (including, but not limited to, extending the visit window, conducting evaluations via video link or phone call, allowing for safety procedures to be conducted at a local facility). The rationale (e.g., the specific limitation imposed by the SARS-CoV-2 infection that led to the inability to perform the protocol-specified assessment) and outcome of the discussion will be documented in the electronic case report form (eCRF).

It is not anticipated that there will be any interaction between DC-806 and any of the currently approved vaccines against SARS-CoV-2 that would lead to an increased risk to the participant above that of receiving such a vaccination without participating in this study. Therefore, both vaccinated and unvaccinated participants are allowed.

3.2.5 Other

For a rationale of the selected dose of DC-806, see Section 3.4.4.

Although no DC-806-related malformations or variations were shown at any dose level in animal studies, the risk of fetal harm of DC-806 in female participants of childbearing potential is not known. To minimize any potential risks, females who are breastfeeding or of childbearing potential will be excluded from the participation in this clinical study.

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The Investigator will take all the usual precautions necessary for studies at an early stage in the development of a new drug.

3.3 Selection of Study Population

Healthy participants are recommended by FDA guidance document for conducting clinical DDI studies unless the study drug has intolerable safety concerns.[10] A total of 28 healthy male and female participants, up to CCI participants in each cohort, are planned to be enrolled in the study, to have approximately CCI evaluable participants in each cohort. No participant will be a part of more than 1 cohort.

3.3.1 Inclusion Criteria

The following inclusion criteria must be met for a participant to be eligible for inclusion in the study:

1. Sex: male or female; females must be of nonchildbearing potential, or postmenopausal.
2. Age: 18 to 55 years, inclusive, at screening.
3. Body mass index (BMI): 18.0 to 32.0 kg/m^2, inclusive, at screening.
4. Weight: ≥50 kg at screening.
5. Status: healthy participants.
6. At screening, females must be of nonchildbearing potential (defined as at least 12 consecutive months with no menses prior to screening, a serum follicle-stimulating hormone (FSH) test to confirm postmenopausal status, or being surgically sterilized); nonpregnancy will be confirmed for all females by a serum pregnancy test conducted at screening, and by a urine pregnancy test at admission and at follow-up.
7. Male participants, if not permanently surgically sterilized, must inform all sexual partners of their participation in a research study and agree to use a highly effective method of contraception and not donate sperm from admission to the clinical site until 30 days after the last study drug administration.
   Adequate contraception for the male participant (and his female partner, if she is of childbearing potential) is defined as using one of the following in combination with a condom: vasectomy, bilateral tubal ligation, hormonal contraceptives or an intrauterine device. Total abstinence from heterosexual intercourse, in accordance with the lifestyle of the participant, is also acceptable.
8. All prescribed medication must have been stopped at least 14 days prior to admission to the clinical site.
9. All over-the-counter medication, vitamin preparations and other food supplements, or herbal medications (e.g., St. John's wort) must have been stopped at least 7 days (or 5 half-lives for certain medications, whichever is longer) prior to admission to the clinical site. Occasional use of acetaminophen/paracetamol (e.g., up to 2 grams per day) is permitted during this period and throughout the study.
10. Ability and willingness to abstain from alcohol-, caffeine-, and methylxanthine- containing beverages or food (e.g., coffee, tea, cola, chocolate, energy drinks) from 48 hours (2 days) prior to admission to the clinical site and during confinement at the clinical site.
11. Willingness to abstain from any strenuous physical exercise from 96 hours (4 days) prior to admission and during confinement at the clinical site.
12. Good physical and mental health on the basis of medical history, physical examination, clinical laboratory assessments, 12-lead ECG, and vital signs, as judged by the Investigator.
13. Willing and able to sign the ICF.

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3.3.2 Exclusion Criteria

Note: Restrictions that apply to the period after admission are described in Section 3.4.8 except when they concern a statement of willingness.

A participant who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Employee of ICON or the Sponsor.
2. History of relevant drug and/or food allergies, in the opinion of the Investigator.
3. Females who are currently breastfeeding.
4. Smoking more than 5 cigarettes, 1 cigar, or 1 pipe daily within 3 months prior to screening.
5. Unwilling or unable to abstain from tobacco products within the 48 hours (2 days) prior to admission and during confinement in the clinical site.
6. History of alcohol abuse or drug addiction (including soft drugs like cannabis products) within 1 year prior to screening.
7. Positive drug and/or alcohol screen (opiates, methadone, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol) at screening or admission to the clinical site.
8. History within the previous 12 months of alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink=12 oz beer, 5 oz wine, and 1.5 oz spirits). Alcohol consumption will be prohibited 48 hours prior to admission to the clinical site and during confinement at the clinical site.
9. Positive screen for HbsAg, HCV antibodies, or HIV 1 and 2 antibodies.
10. Consumption of any nutrients known to modulate CYP450 enzymes activity (e.g., grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) within 14 days prior to the first administration of study drug and during the study (including washout period/clinic furlough until after discharge in the last study period).
11. Participation in a drug study within 30 days prior to study drug administration in the current study. Participation in 4 or more other drug studies in the 12 months prior to study drug administration in the current study.
12. History of donation of more than 450 mL of blood within 60 days prior to dosing in the clinical site or planned donation before 30 days has elapsed since intake of study drug.
13. Plasma or platelet donation within 7 days of dosing and through follow-up.
14. Significant and/or acute illness within 5 days prior to study drug administration that may impact safety assessments, in the opinion of the Investigator.
15. Unsuitable veins for infusion or blood sampling as determined by the Investigator or study staff.
16. Any other condition or prior therapy that, in the Investigator's opinion, would confound or interfere with the evaluation of safety, tolerability, or PK of the study drug, interfere with study compliance, or preclude informed consent.

3.3.3 Removal of Participants from the Study or Assessment

Participation in the study is strictly voluntary. A participant has the right to withdraw from the study at any time for any reason.

The Investigator has the right to terminate participation of a participant for any of the following reasons: difficulties in obtaining blood samples, violation of the protocol, severe AEs or SAEs, or for any other reason relating to the participant's safety or integrity of the study data.

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If a participant is withdrawn from the study, the Sponsor/study monitor will be informed immediately (within 1 business day). If there is a medical reason for withdrawal, the participant will remain under the supervision of the Investigator until satisfactory health has returned.

After signing informed consent, participants who drop out or withdraw for any reason without completing all screening evaluations successfully as well as participants who drop out or withdraw prior to the first dose of study drug will be considered screening failures. Screen failures will not be entered into the database for this study.

A participant who is withdrawn or voluntarily withdraws from the study for any reason, whether related to the study drug(s) or not, after having received the first dose of study drug(s), will be considered an early termination participant. If a participant is withdrawn for a reason related to the study drug(s), according to the judgment of the Investigator, the early termination participant will not be replaced. If a participant does not complete the study for a reason not related to the study drug(s), the early termination participant may be replaced after mutual agreement between the Sponsor and ICON. The decision regarding the replacement of participants will be documented.

ICON will make every effort to ensure that early-termination participants who have received study drug(s) complete the early termination assessments/safety follow-up assessments.

3.3.3.1 Stopping Rules for Individual Participants

Dosing of a participant will be stopped at any time during the study if any of the following circumstances occurs:

- A drug-related serious adverse reaction (i.e., an SAE considered at least possibly related to the study drug(s) administration).
- A drug-related severe adverse reaction (i.e., severe nonserious AEs considered at least possibly related to the study drug(s) administration).
- Other findings that, at the discretion of the Investigator and/or Sponsor's Medical Monitor, indicate that further dosing should be stopped.

3.4 Treatments

3.4.1 Treatments Administered

The following treatments are planned to be administered:

Cohort 1 (n = CCI	Probe substrate cocktail includes midazolam (CYP3A4 substrate) and repaglinide (CYP2C8 substrate)
Period 1:	A single oral dose of the 2-probe substrate cocktail consisting of CCI mg midazolam and CCI mg repaglinide administered under fasted conditions in the morning on Day 1
Period 2:	Twice-daily oral doses of CCI mg DC-806 administered 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 in the morning of Day 7 under fasted conditions, 1.5 hours (±15 min) after DC-806 dosing, while DC-806 BID dosing will be continued until the end of Day 8 (final dose given in the evening of Day 8)

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Cohort 2 (n = CCI)	Probe substrate cocktail includes digoxin (P-gp substrate) and rosuvastatin (BCRP/OATP1B1 substrate)
Period 1:	A single oral dose of the 2-probe substrate cocktail consisting of CCI mg digoxin and CCI mg rosuvastatin administered under fasted conditions in the morning on Day 1
Period 2:	Twice-daily oral doses of CCI mg DC-806 administered 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 in the morning of Day 8 under fasted conditions, 1.5 hour (±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)

3.4.2 Identity of Investigational Product(s)

Active Investigational Medicine

Active substance	DC-806
Activity	CCI
Strength	CCI mg
Dosage form	CCI
Manufacturer	Patheon Pharmaceuticals Inc. (Thermo Fisher Scientific Inc.)

Probe Substrate

Active substance	Midazolam
Activity	Short-acting benzodiazepine central nervous system depressant, used as CYP3A4 probe substrate
Strength	CCI mg/mL
Dosage form	Oral Syrup
Manufacturer	Sourced by pharmacy at ICON

Probe Substrate

Active substance	Repaglinide
Activity	Insulin secretagogue, used as CYP2C8 probe substrate
Strength	CCI mg
Dosage form	Oral Tablet
Manufacturer	Sourced by pharmacy at ICON

Probe Substrate

Active substance	Digoxin
Activity	Cardiac Glycoside, inhibits sodium-potassium ATPase of the myocyte, used as p-glycoprotein probe substrate
Strength	CCI mg
Dosage form	Oral Tablet
Manufacturer	Sourced by pharmacy at ICON

Probe Substrate

Active substance	Rosuvastatin

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Activity	HMGCoA reductase inhibitor, used as BCRP/OATP1B1 probe substrate
Strength	[redacted] mg
Dosage form	Oral Tablet
Manufacturer	Sourced by pharmacy at ICON

For details concerning drug storage and drug accountability see Appendix 8.1.

3.4.3 Method of Assigning Screening / Participant Number to Participants

Participants will receive a unique screening number and will be screened according to the inclusion and exclusion criteria under provision of an informed consent. Participants who have met all eligibility criteria will receive a participant number upon inclusion in the study and prior to dosing. Details on the participant numbering method will be described in the instructions provided to the clinical site.

After signing informed consent, participants who drop out or withdraw for any reason without completing all screening evaluations successfully as well as participants who drop out or withdraw prior to the first dose of study drug will be considered screening failures.

3.4.4 Selection of Doses Used in the Study

DC-806

The CCI mg BID dose of DC-806 will be used in this DDI study. The CCI mg BID dose is the highest clinically relevant DC-806 dose to be evaluated in future studies thus providing the highest DC-806 exposure at steady state to maximize the potential perpetrator DDI effect of DC-806 in this study. This dose level is also supported with adequate clinical safety data from the completed DC-806 phase I study where CCI mg BID was administered for up to 7 or 28 days in healthy participants or participants with psoriasis, respectively, and was generally well tolerated. Together, the nonclinical toxicology profile of DC-806 and clinical data collected to date for DC-806 support the present study. Since CCI mg BID is the highest dose of DC-806 in future clinical studies, the results achieved in this study will adequately characterize the DDI potential of DC-806 as a perpetrator and will inform future clinical study protocols.

Midazolam

The use of midazolam as a CYP3A4 substrate has been validated for assessment of DDIs. The [redacted] mg dose is within the dosing range approved for therapeutic use and commonly used in studies evaluating potential DDIs with midazolam and has been shown to be safe and well tolerated in healthy participants where up to CCI increase in C_{max} and CCI increase in AUC of midazolam were observed due to the DDI effect.[8] Using the net effect model[9] and IC_{50} value obtained from *in vitro* assessment of DC-806 as a CYP3A4 inhibitor, it is predicted that DC-806 may potentially cause a CCI increase in midazolam exposure, which is well within safe and well tolerated exposure levels reported in healthy participants and hence is considered appropriate for this study.[8,12]

Repaglinide

The use of repaglinide as a CYP2C8 substrate has been validated for assessment of DDIs. The CCI mg dose has been shown to be safe and well tolerated in healthy participants[8] and is considered appropriate for this study. Using the net effect model[9] and IC_{50} value obtained from in vitro assessment of DC-806 as a CYP2C8 inhibitor, it is predicted that DC-806 may potentially cause a CCI increase in repaglinide exposure which is similar to results of a tucatinib DDI study where

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repaglinide exposure following a CCI mg dose was increased by CCI (AUC) and CCI (C_{max}) in healthy participants and was well tolerated.[8]

Digoxin

The use of digoxin as a P-gp substrate has been validated for assessment of DDIs. A dose of up to CCI mg has been shown to be safe and well tolerated in healthy participants and is considered appropriate for this study.[8] A CCI increase in AUC and a CCI increase in C_{max} of digoxin following a CCI mg dose was well tolerated in healthy participants in the tucatinib DDI study, thereby demonstrating a good safety profile,[8] However, a lower dose of CCI mg digoxin was selected for this study since this is the digoxin dose evaluated/validated in a cocktail study showing no interaction between digoxin and rosuvastatin.[12]

Rosuvastatin

The use of rosuvastatin as a BCRP/OATP1B1 substrate has been validated for assessment of DDIs. The CCI mg dose is the lowest dose within the FDA approved dose range of CCI mg daily for adults[5] and has been shown to be safe and well tolerated in healthy participants.[11,12] Hence, the CCI mg single dose is considered appropriate for this study.

3.4.5 Study Drug Administration

For both cohorts of the study, study drugs will be administered with the participant in the upright position. Study drug(s) will be swallowed with approximately 240 mL water (room temperature). Study drugs should not be crushed, chewed, or dissolved.

The probe substrate cocktail will be administered to participants in the morning after an overnight fast of at least 10 hours relative to probe substrate cocktail dosing. Fasting will continue for a period of at least 4 hours after probe substrate cocktail dosing.

DC-806 BID dosing is to be employed in both cohorts, DC-806 doses will be administered once every 12 hours (± 30 minutes) 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 in dosing Period 2 (for both Cohorts 1 and 2) as described below.

On Day 7 (Cohort 1) or Day 8 (Cohort 2), the morning dose of DC-806 will be administered 1.5 hour before the probe substrate cocktail dose under fasted conditions. Evening doses on Day 7 (Cohort 1) or Day 8 (Cohort 2) and all other DC-806 doses will be dosed under fed conditions. The timing of the morning and evening doses of DC-806 is approximately the same throughout the DC-806 dosing period.

Administration of the study drug(s) will be supervised by the Investigator or authorized designee. A mouth and hand inspection will take place after drug administration.

Cohort 1:

Each participant will receive a single oral dose of the 2-probe substrates (midazolam and repaglinide, administered as a cocktail) in the morning on Day 1 of Period 1 after an overnight fast of at least 10 hours following standard dinner on the evening before. Fasting will continue for a period of at least 4 hours after administration of the 2-probe substrate cocktail, i.e., until scheduled lunch. During fasting, no fluids are allowed except water; however, water is not allowed from 1 hour predose

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until 1 hour postdose (apart from the water taken with the dose as described above). When not fasting, noncaffeinated fluids are allowed ad libitum.

In Period 2, (starting on Day 4) participants will receive CCI mg of DC-806 BID administered under fed conditions on Days 4 through 8 except for the morning dose on Day 7 when dosing of DC-806 is under fasted conditions after an overnight fast of at least 10 hours (relative to probe substrate dosing time) following standard dinner on the evening before. A single oral dose of the 2-probe substrate cocktail (midazolam and repaglinide) will be administered under fasted conditions, 1.5 hours (±15 min) after DC-806 dosing in the morning of Day 7 after an overnight fast of at least 10 hours following standard dinner on the evening before, while DC-806 BID dosing will be continued until the end of Day 8 (final dose given in the evening of Day 8). Fasting on Day 7 will continue for a period of at least 4 hours after administration of the 2-probe substrate cocktail, i.e., until scheduled lunch. During fasting, no fluids are allowed except water; however, water is not allowed from 1 hour predose until 1 hour postdose (apart from the water taken with the dose as described above). When not fasting, noncaffeinated fluids are allowed ad libitum.

For Cohort 1, dosing time of the 2-probe substrate cocktail is referenced as time 0 and is the same for both Periods 1 and 2. The dosing of the 2-probe substrate cocktail in Period 2 will be 1.5 hr after DC-806 dose in the morning (i.e. DC-806 to be dosed at -1.5 hr). Overnight fasting is required for DC-806 morning administration on Day 7 only.

Cohort 2:

Each participant will receive a single oral dose of the 2-probe substrates (digoxin and rosuvastatin, administered as a cocktail) under fasted conditions in the morning on Day 1 of Period 1 after an overnight fast of at least 10 hours following standard dinner on the evening before. Fasting will continue for a period of at least 4 hours after administration of the 2-probe substrate cocktail, i.e., until scheduled lunch. During fasting, no fluids are allowed except water; however, water is not allowed from 1 hour predose until 1 hour postdose (apart from the water taken with the dose as described above). When not fasting, noncaffeinated fluids are allowed ad libitum.

In Period 2 (starting on Day 5), participants will receive CCI mg of DC-806 BID administered under fed conditions on Day 5 through Day 9 except for the morning dose on Day 8 when dosing of DC-806 is under fasted conditions after an overnight fast of at least 10 hours (relative to probe substrate dosing time) following standard dinner on the evening before. A single oral dose of the 2-probe substrate cocktail (digoxin and rosuvastatin) will be administered under fasted conditions, 1.5 hour (±15 min) after DC-806 dosing, in the morning of Day 8 after an overnight fast of at least 10 hours following standard dinner on the evening before, while DC-806 BID dosing will be continued until the end of Day 9 (final dose given in the evening of Day 9). Fasting on Day 8 will continue for a period of at least 4 hours after administration of the 2-probe substrate cocktail, i.e., until scheduled lunch. During fasting, no fluids are allowed except water; however, water is not allowed from 1 hour predose until 1 hour postdose (apart from the water taken with the dose as described above). When not fasting, noncaffeinated fluids are allowed ad libitum.

For cohort 2, dosing time of the 2-probe substrate cocktail is referenced as time 0 and is approximately the same for both periods 1 and 2. The dosing of 2-probe substrate cocktail in Period 2 will be 1.5 hr after DC-806 dose in the morning of Day 8 (i.e. DC-806 to be dosed at -1.5 hr). Overnight fasting is required for DC-806 morning administration on Day 8 only.

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3.4.6 Meals During the Study

With the exception of the restrictions with respect to methylxanthine- and alcohol- containing beverages or food as described in Section 3.4.8 and what has been described in Section 3.4.4, there are no special requirements related to food and beverage intake. When not fasting, meals and snacks (such as decaffeinated coffee, herbal tea, fruit, biscuits) will be provided according to the clinical site standard operating procedures (SOPs). A standard dinner will be provided on the evening before those days where fasting is required until lunch time.

3.4.7 Blinding

This is an open-label study.

3.4.8 Concomitant Medication and Other Restrictions During the Study

Note: Restrictions that apply to the period before admission are described in Section 3.3.1 and Section 3.3.2.

3.4.8.1 Concomitant Medication

The use of all prescribed medication is not allowed from admission to the clinical site until follow-up. The use of all over the counter medication (e.g., Ibuprofen, Claritin), vitamin preparations and other food supplements, or herbal medications (e.g., St. John's wort) is not allowed from admission to the clinical site until follow-up. An exception is made for acetaminophen: from admission onward, the Investigator may permit up to 2 g/day (based on inclusion criteria) of acetaminophen for the treatment of headache or any other pain. Other medication to treat AEs may only be prescribed if deemed necessary by the Investigator. If medication is used, the name of the drug, the dose, and dosage regimen will be recorded in the eCRF.

3.4.8.2 Contraception

Male participants are required to use adequate contraception (see description below) and not donate sperm from admission to the clinical site on Day -1 until 30 days after the last dose of study drug(s) administration. Adequate contraception for the male participant (and his female partner, if she is of childbearing potential) is defined as using one of the following methods below in combination with a condom:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine hormone-releasing system

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- Implantable intrauterine device
- Surgical sterilization (e.g., vasectomy [male participants only], bilateral tubal occlusion/ligation [female partner of male participant])
  - For vasectomy, the procedure should be documented in the participants' medical history
- Total abstinence from heterosexual intercourse, in accordance with the lifestyle of the male participant, is also acceptable.

For male participants with female partners who are of non-childbearing potential or who are already pregnant, or with male partners, there is a risk of drug exposure through the ejaculate that might be harmful to the sexual partners. Therefore, these male participants must use a condom from Day -1 until ≥30 days after the last dose of study drug(s) administration.

A female is considered of childbearing potential when fertile following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for ≥12 consecutive months without an alternative medical cause. Females of childbearing potential are not allowed in this study.

3.4.8.3 Other Restrictions

The use of alcohol is not allowed during confinement at the clinical site or within 48 hours (2 days) prior to Day -1.

The use of methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks), and grapefruit (juice) and tobacco products is not allowed during confinement at the clinical site.

Strenuous exercise is not allowed during confinement at the clinical site.

Participants must not donate blood during the study until ≥30 days after study drug administration (other than the blood sampling planned for this study).

3.4.9 Treatment Compliance

Study drugs will be administered in the clinical site. To ensure treatment compliance, administration of the study drugs will be supervised by the Investigator or authorized designee. Compliance will be further confirmed by bioanalytical assessment of DC-806 in plasma samples (see Section 3.5.3). The exact times of study drug administration and the number of units administered will be recorded in the eCRF.

3.5 Pharmacokinetic, Safety, and Exploratory Assessments

3.5.1 Pharmacokinetic, Safety, Exploratory and Schedule(s) of Assessments

Schedules of assessments are presented in Table 1 and Table 2.

3.5.1.1 Pharmacokinetic Assessments

A schedule of sampling for PK assessments is presented in Table 3, Table 4, Table 5 and Table 6.

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3.5.1.1.1 Blood Sampling

At the time points defined in the schedule of assessments (Table 1 and Table 2) and schedule of sampling for PK assessments (Table 3-6), blood samples will be taken for the analysis of DC-806, midazolam and its metabolite, 1-hydroxymidazolam, repaglinide, digoxin and rosuvastatin in plasma samples. The blood samples will be taken via an indwelling IV catheter or by direct venipuncture. The exact times of blood sampling will be recorded in the eCRF. Details on sample collection, handling, storage, and shipping will be described in the laboratory manual prepared by ICON.

3.5.1.2 Safety and Tolerability Monitoring

Monitoring for safety and tolerability will consist of AE assessments, clinical laboratory assessments, vital signs, 12-lead ECGs, and physical examinations. Assessments will be performed in accordance with the schedules of assessments.

3.5.1.2.1 Adverse Events

After informed consent has been obtained but before initiation of study drugs, only SAEs caused by a protocol-mandated intervention should be collected and reported to the Sponsor. The SAE Notification Form provided to Investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., ≤24 hours after learning of the event), using the contact information provided in the Investigator site file.

After initiation of study drugs, all AEs will be reported until study follow-up. Any clinically significant observations, as determined by the Investigator, in results of clinical laboratory assessments, 12-lead ECGs, vital signs, or physical examinations will be recorded as AEs.

A TEAE is defined as any event not present prior to administration of the study drug(s) or any event already present that worsens in either severity or frequency following exposure to the study drug(s).

At several time points before and after study drug administration, participants will be asked nonleading questions to determine the occurrence of AEs/SAEs. Participants will be asked in general terms about any AEs at regular intervals during the study. In addition, all AEs reported spontaneously after study drug administration during the course of the study will be recorded. All answers will be interpreted by the Investigator using the Medical Dictionary for Regulatory Activities (MedDRA; most recent version) for AEs and will be recorded in the eCRF as reported terms.

The severity of the AEs will be graded as mild, moderate, or severe; the relationship between the AEs and the study drugs will be assessed as not related, unlikely related, possibly related and related (refer to Section 8.2.1.1). Details on grading of the severity of AEs and causality (relationship to study drug) are given in Appendix 8.2.1.2.

Pregnancy of female participants and female partners of male participants will be monitored along with follow-up, if warranted (see Appendix 8.3).

3.5.1.2.2 Clinical Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected according to the clinical site SOPs. All blood and urine specimens will be sent to a local reference laboratory for analysis and testing.

The following parameters will be measured:

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- Hematology: erythrocytes (red blood cells), leukocytes (white blood cells) with differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils), hemoglobin, hematocrit, and platelet count.
- Coagulation: prothrombin time/international normalized ratio (PT/INR) will be measured at screening only.
- Blood chemistry: sodium, potassium, chloride, bicarbonate, creatinine, creatine kinase (CK), amylase, lipase,, blood urea nitrogen (BUN), albumin, calcium, magnesium, inorganic phosphorus, alkaline phosphatase, AST (aspartate aminotransferase), ALT (alanine aminotransferase), fractionated bilirubin (total, direct, and indirect), total protein, total cholesterol, high density lipoprotein (HDL), LDL, triglycerides, and uric acid. Estimated creatinine clearance (calculated using the Cockcroft-Gault Formula) and thyroid stimulating hormone (TSH) will be measured at screening only. Fasting glucose will be measured for both Cohorts 1 and 2 as part of clinical chemistry, however only Cohort 1 will have additional blood glucose monitoring using glucometer at designated timepoints post repaglinide dosing due to potential effect of repaglinide on glycemic control.
- Urinalysis: A midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, leukocyte esterase, and pH (to be captured in the database). Microscopic analysis will only be performed when results are positive for occult blood, protein, or leukocyte esterase.

The following parameters will also be measured:

- Urine will be collected for the assessment of the following drugs of abuse: opiates (including morphine and oxycodone), methadone, cocaine, amphetamines (including ecstasy and methamphetamine), cannabinoids, barbiturates, PCP, benzodiazepines, tricyclic antidepressants, nicotine metabolites [cotinine], and alcohol. Results must be available and reviewed before dosing on Day 1.
- Serology will be collected for the measurement of HIV-1 and -2 antibodies, hepatitis B surface antigen, and hepatitis C antibody.
- For all females, a serum/urine pregnancy test will be collected. Results must be available and reviewed before dosing on Day 1.
- A FSH panel will be performed on all postmenopausal females prior to dosing on Day 1.

In case of unexplained or unexpected clinical laboratory test values for enrolled participants, the tests will be repeated as soon as possible and followed up until the results are considered not clinically significant, as determined by the Investigator and/or an adequate explanation for the abnormality is found. The clinical laboratory will clearly mark all laboratory test values that are outside the reference range, and the Investigator will indicate which of these deviations are clinically significant. These clinically significant laboratory result deviations will then be recorded as AEs and the relationship to the treatment will be indicated (see also Appendix 8.2).

The procedures for the collection, handling, and shipping of laboratory samples are specified in the laboratory manual(s) provided to the clinical site.

The procedures for the collection, handling, and shipping of laboratory samples are specified in the laboratory manual(s) provided to the clinical site.

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3.5.1.2.3 Vital Signs

Systolic and diastolic blood pressure and pulse will be recorded after the participant has been resting for at least 5 minutes in the supine position. These assessments will be made using an automated device whenever possible. Body temperature, pulse oximetry (Cohort 1 only) and respiratory rate will also be measured.

3.5.1.2.4 Electrocardiogram

A standard 12-lead ECG will be recorded after the participant has been resting for at least 5 minutes in the supine position. 12-lead ECGs will be performed either as single ECGs or in triplicate at timepoints indicated in the schedules of assessments (Table 1 and Table 2). At each time point, all individual captures of the triplicate 12-lead ECGs set will be conducted within 5 minutes between the first and the third ECG. The ECG will be recorded using an ECG machine equipped with computer -based interval measurements. The following ECG parameters will be recorded: heart rate, PR interval, QRS-duration, QT-interval, QTc-interval (Fridericia's) and the interpretation of the ECG profile by the Investigator. Safety assessment and PK sampling need to be performed after the triplicate ECG assessment.

3.5.1.2.5 Physical Examination

As indicated in the schedules of assessments (Table 1 and Table 2) complete physical examination will be performed consisting of all body systems (with the exception of genitalia, anus/rectal, and breast examinations, which will only be performed if medically indicated). Unscheduled symptom--driven physical examinations may be conducted at any time per the Investigator's discretion.

3.5.1.2.6 Columbia-Suicide Severity Rating Scale

Suicide-related thoughts and behaviors will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening in Cohort 1 of the study.

The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period.[12,13,14] The scale includes suggested questions to solicit the type of information needed to determine if a suicide related thought or behavior occurred. The C-SSRS will be administered by appropriately trained site personnel. A referral to a psychiatrist will be made in case of a significant finding on the C-SSRS.

All AEs obtained through the questionnaire will be recorded. The Sponsor or its designee will be alerted within 24 hours of the Investigator's awareness of any SAEs from these questionnaires.

3.5.1.3 Exploratory Assessments

At the time points defined in the schedules of assessments, blood samples will be collected to CCI

3.5.1.4 Total of Blood Volume

The total volume of blood drawn for a participant will not surpass 525 mL (except when extra blood samples need to be taken for safety reasons).

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3.5.2 Appropriateness of Assessments

The assessments that will be made in this study are standard, consistent with regulatory guidelines, and generally recognized as reliable, accurate, and relevant.

3.5.2.1 Timing of Assessments

If more than one procedure is required at the same time point, the procedures will be conducted as close as possible to the nominal time point, with the order of procedures determined at the Investigator's discretion. The order of the assessments should be arranged in such a way that PK blood sampling will be done after the ECG and vital signs recordings have been conducted, with PK blood sampling exactly on time (within the allowed window).

3.5.3 Drug Concentration Measurements

The analysis of DC-806, midazolam, 1-hydroxymidazolam, repaglinide, digoxin and rosuvastatin concentrations in plasma samples will be performed using validated liquid chromatography-mass spectrometry/mass spectrometry methods.

The bioanalytical reports will be included in the clinical study report as an appendix.

3.5.4 Retention of Blood and Urine Samples

Blood and urine samples remaining after clinical laboratory assessments have been performed will not be stored for future use and will be destroyed after analysis as per laboratory procedure.

After PK assessments have been performed, any remaining blood samples will be stored at the Sponsor (or another facility under responsibility of the Sponsor) for future research related to this clinical study including, but not limited to, drug metabolism and PK analyses of DC-806. The samples will be stored for a maximum period of 5 years, after which the samples will be destroyed.

3.6 Statistical Procedures and Determination of Sample Size

3.6.1 Analysis Sets

3.6.1.1 Safety Set

All participants who have received at least 1 dose of DC-806, midazolam, repaglinide, digoxin or rosuvastatin.

3.6.1.2 Pharmacokinetic Set

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.

3.6.2 Statistical and Analytical Plan for PK, Safety, and Exploratory Evaluation

Descriptive statistics will be used for all relevant PK parameters: n, mean, SD, coefficient of variation (CV), minimum, median, maximum, geometric mean, CV of geometric mean.

The effect of DC-806 on the PK of each of the probe substrates midazolam (and its active metabolite, 1-hydroxymidazolam), repaglinide, digoxin and rosuvastatin will be analyzed separately.

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The geometric mean ratio and associated CCI % CI of each probe substrate administered with DC-806 compared with the probe substrate dosed alone will be calculated for C_{max}, AUC_{0-t}, and AUC_{0-inf}. These values will be estimated from a linear mixed-effects model on the natural log-transformed value of the parameter including a fixed effect for treatment and a random subject-level effect and presented along with the model estimates of least-squares geometric mean values in each treatment period.

CCI [redacted] will be reported by the descriptive statistics.

A statistical analysis plan (SAP) will be generated by the Biostatistics Department of ICON; the SAP will be finalized prior to database lock. Full details of the analysis to be performed will be included in the SAP. Any deviation from the SAP will be reported in the section "Changes in Planned Analysis" in the CSR.

3.6.2.1 Pharmacokinetic Evaluation

PK endpoints will be the plasma PK parameters of midazolam (and its active metabolite, 1-hydroxymidazolam), repaglinide, digoxin and rosuvastatin, as well as for DC-806 at steady state. The PK parameters calculated using noncompartmental analysis from the plasma -concentration time data for DC-806, midazolam and its active metabolite, 1-hydroxymidazolam, repaglinide, digoxin and rosuvastatin include, but are not limited to, the parameters as given in Table 7. A complete list of PK parameters will be provided in the SAP.

Table 7 Pharmacokinetic Parameters

Parameter	Description
C_{max}	Maximum observed plasma concentration
t_{max}	Time to attain maximum observed plasma concentration
AUC_{0-t}	Area under the plasma concentration-time curve up to time t, where t is the last point with concentrations above the lower limit of quantification (LLOQ)
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
k_{el}	Terminal elimination rate constant
$t_{1/2}$	Terminal elimination half-life, calculated as $0.693/k_{el}$
CL/F	Apparent oral clearance, calculated as dose/AUC_{0-inf}
V_z/F	Apparent volume of distribution at terminal phase
$C_{max,ss}$	Maximum observed plasma concentration at steady state (DC-806 only)
$C_{trough,ss}$	Concentration observed at steady state immediately before the next dose is administered (DC-806 only)
$AUC_{0-tau,ss}$	Area under the plasma concentration-time curve over a dosing interval tau at steady state (DC-806 only)
$t_{max,ss}$	Time to attain maximum observed plasma concentration at steady state (DC-806 only)

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All data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

3.6.2.2 Evaluation of Safety and Tolerability

Demographics (age, sex, ethnicity, and race) and baseline characteristics (height, weight, and BMI) will be summarized. Medical history and prior and concomitant medications will be provided in data listings. Safety and tolerability will be assessed through reports of AEs, clinical laboratory data, vital sign, ECG and physical examination parameters, as well as any other parameter that is relevant for safety analysis.

3.6.2.2.1 Adverse Events

Summary tables of TEAEs will be presented by system organ class based on the MedDRA terminology list (preferred terms): a table containing the number of participants experiencing the AE by treatment, a table by treatment and relationship, and a table by treatment and severity.

3.6.2.2.2 Clinical Laboratory

Clinical laboratory data will be listed accompanied by an indication if the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable.

3.6.2.2.3 Vital Signs Electrocardiogram and Physical Examination Parameters

Vital sign and ECG parameters will be listed and presented descriptively, where applicable. Physical examination parameters will be presented in listings only.

3.6.2.3 Exploratory Evaluation

CCI [redacted] will be reported by the descriptive statistics.

3.6.3 Determination of Sample Size

A total of approximately 28 healthy male and female participants will be enrolled in the study with up to CCI to be enrolled in each cohort, aiming to have approximately CCI evaluable participants per cohort assuming a CCI% drop out. For this study, no formal sample size calculation was done because the extent of the potential interaction effect is unknown. The sample size of 28 participants (CCI 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.

3.7 Data Quality Assurance

The study may be audited by the Quality Assurance Department at ICON to assess adherence to the CSP and Quality System. During the conduct of the study, process-related audits may be performed. An audit certificate outlining any audits and other related activities performed may be provided in the appendices of the final CSR.

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The clinical site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study is conducted according to the relevant regulatory requirements. The eCRF entries will be verified with the source documentation, if applicable.

Regulatory authorities, the Institutional Review Board (IRB), and/or the Sponsor may request access to all source documents, eCRFs, and other study documentation for purposes of an on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed at ICON for all documents that are generated in relation with the study.

An explanation will be given for all missing, unused, and spurious data in the relevant sections of the CSR. Details on the handling of such data will be included in the SAP.

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4. ETHICS

4.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments.[16]

This study is also designed to comply with International Council for Harmonisation (ICH) E6(R2) Guideline for Good Clinical Practice (GCP) (European Medicines Agency [EMA]/Committee for Medicinal Products for Human Use [CHMP]/ICH/135/1995)[17] and any applicable national and local laws and regulations (e.g., Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314).

Guidelines adopted by the ICH and other relevant international guidelines, recommendations, and requirements will be taken into account as comprehensively as possible, as long as they do not violate local law.

Whenever the term "Investigator" is noted in the CSP text, it may refer to either the Investigator at the site or an appropriately qualified, trained, and delegated individual of the investigational site.

4.2 Institutional Review Board

The CSP and the ICFs will be submitted for review and approval by an IRB prior to the eligibility screening. The composition of the IRB will be in accordance with the recommendations of the ICH E6(R2) GCP.[17]

ICON will keep the IRB informed about the progress of the study. All changes in research activities and all unanticipated problems involving risks to human participants will be immediately reported in accordance with IRB requirements. ICON will inform the participants and the IRB if anything occurs on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal, or if further recruitment of participants in the study has been put on hold for that reason, whichever occurs first. The study may be suspended pending further review by the IRB, except insofar as suspension would jeopardize the participants' health. ICON will take care that all participants are kept informed.

No changes will be made in the study without IRB approval, except when required to eliminate apparent immediate hazards to human participants.

Notification of the end of the study will be sent to the IRB within 90 days of database lock. In case a study is temporarily halted, ICON will notify the IRB immediately, including the reason for this. In case a study is ended prematurely, the IRB will be notified within 15 days, including the reasons for the premature termination. The end of the study is defined as the date of receipt of the last data point for statistical analysis of the last participant participating in the study.

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4.3 Participant Information and Consent

All participants will be informed verbally and in writing regarding the objectives, procedures and risks of study participation. The participants will sign the ICF that contains information about the objectives of the study, the procedures followed during the study, and the risks and restrictions of the study, with special reference to possible side effects of the study drug and potential interactions. In the event new information becomes available (e.g., change in the risk-benefit profile, identification of new risk(s), study procedures added, modified, or removed, etc.), participants will be provided the updated information as appropriate and given the option to reaffirm their consent if applicable (i.e., an updated IRB approved ICF).

4.4 Privacy

All personal details of participants will be treated as confidential by the Investigator and staff at ICON, and handling of personal data will be in compliance with the Health Insurance Portability and Accountability Act of 1996.[18]

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5. STUDY ADMINISTRATIVE STRUCTURE

5.1 Documentation

5.1.1 Archiving

The Investigator shall retain essential documents for a period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor will inform the Investigator/institution as to when these documents no longer need to be retained.

5.1.2 Recording of Data in Source Documents and Electronic Case Report Forms

All data will be collected on source documents and then entered in the eCRFs.

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6. CONFIDENTIALITY AND PUBLICATION POLICY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB personnel, the Sponsor, and its authorized representatives are allowed full access to the records.

All study participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participants, who will be required to give consent for their data to be used as described in the ICF. The participants must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Identification of participants and eCRFs shall be by unique participant numbers only.

All personal details will be treated as confidential by the Investigator and staff at ICON.

All relevant aspects regarding publication will be part of the contract (or similar document) between the Sponsor and ICON.

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7. REFERENCES

1. DICE Therapeutics, Inc. Investigator's Brochure DC-806 Version 2.0, dated 18 Jan 2023
2. Drug Label Information (2023) - Midazolam Hydrochloride Syrup CIV. Padagis US, LLC. Link: https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0be63f63-6a93-4782-8f9c-d13ca5ae44bd. Accessed: 10 Jun 2023.
3. Drug Prescribing Information (2023) - Repaglinide Oral Tablets. Novo Nordisk, Inc. Link: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020741s035lbl.pdf. Accessed: 10 Jun 2023.
4. Drug Prescribing Information (2023) - LANOXIN (digoxin) tablets, for oral use. Concordia Laboratories, Inc. Link: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020405s013lbl.pdf. Accessed: 10 Jun 2023.
5. Drug Label Information (2023) - Crestor (rosuvastatin) tablets for oral use. AstraZeneca Pharmaceuticals LP. Link: https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=bb0f3b5e-4bc6-41c9-66b9-6257e2513512.
6. Ryu JY, Song IS, Sunwoo YE, Shon JH, Liu KH, Cha IJ, Shin JG. Development of the "Inje cocktail" for high-throughput evaluation of five human cytochrome P450 isoforms in vivo. Clinical Pharmacology & Therapeutics. 2007 Nov;82(5):531-40.
7. Drug-drug Interaction Study of Ganaplacide and Lumefantrine With Midazolam, Repaglinide, Dextromethorphan,Metformin, Rosuvastatin and Dolutegravir. https://clinicaltrials.gov/study/NCT05236530
8. Topletz-Erickson A, Lee A, Rustia E, Sun H, Mayor J, Abdulrasool L, Walker L and Endres C. Evaluation of Safety and Clinically Relevant Drug–Drug Interactions with Tucatinib in Healthy Volunteers. Clinical Pharmacokinetics (2022) 61:1417–1426.
9. U.S. Food & Drug Administration. In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry. Clinical Pharmacology. January 2020. Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/in-vitro-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions. Accessed at: 10 Jun 2023.
10. U.S. Food & Drug Administration, Center for Drug Evaluation and Research (CDER), Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry. Clinical Pharmacology. Jan 2020. Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions.
11. U.S. Food & Drug Administration. Drug Development and Drug Interaction | Table of Substrates, Inhibitors and Inducers. Aug 2022. Link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers Accessed at: 10 Jun 2023.
12. Ishii Y, Ito Y, Matsuki S, Sanper K, Ogawa O, Takeda K, Schuck E, Uemura N. Clinical Drug-Drug Interaction Potential of BFE1224, Prodrug of Antifungal Ravuconazole, Using Two Types of Cocktails in Healthy Subjects. Clin Transl Sci. 2018; 11: 477-486.
13. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-43.

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DocUUID : a785e6ff-73f2-466b-b8ee-a72ef8469a10

14. Posner K. 2007. State of the Science: Measurement of Suicidal Adverse Events and The Columbia Suicide Severity Rating Scale. NCDEU: Boca Raton, FL.
15. Posner K, Melvin GA, Stanley B, Oquendo MA, Gould M. Factors in the assessment of suicidality in youth. CNS Spectr. 2007;12(2):156-62.
16. World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants (18th WMA General Assembly 1964), revised at 64th WMA General Assembly, Fortaleza, Brazil, Oct 2013.
17. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E6(R2): Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice. Guidance for Industry, Adopted by the U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Mar 2018.
18. Health Insurance Portability and Accountability Act of 1996. Public Law 104 191, 104th Congress.
19. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Guideline for Industry, Adopted by the Food and Drug Administration (FDA), Mar 1995.

Note: the study drug(s) being administered at the site contains the same active ingredient as the reference(s) provided above but may be a generic version of that drug (different manufacturer).

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8. APPENDICES

8.1 Drug Accountability

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (eg, Drug Accountability Forms) and disposition (eg, Drug Dispensing Forms) of the study drug must be maintained. The Drug Dispensing Form(s) must be kept current and should contain the following information:

- The identification of the participant to whom the study drug was administered
- The date(s) and quantity of the study drug administered to the participant (when applicable)
- The date(s) and quantity of the study drug returned by the participant (when applicable)

All records and drug supplies must be available for inspection by the monitor at every monitoring visit. Unused medication will be returned to the Sponsor at the end of the study or will be locally destroyed according to study site procedures following Sponsor permission. ICON will retain the original, completed Drug Dispensing Form(s) and Drug Accountability Form(s), and copies will be returned to the Sponsor upon request. The investigator's copy of the Drug Accountability Form(s) must accurately document the return of all study drug supplies to the Sponsor if applicable.

8.2 Adverse Events and Serious Adverse Events Evaluation and Reporting

8.2.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AE definitions will be followed as stated in the "Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (ICH topic E2A).[19]

All AEs reported by the participants or apparent from their physical appearance during the clinical study will be reported on the AE eCRF page.

8.2.1.1 Adverse Event Causality Assessment

The Investigator is obligated to assess the relationship between the study drug(s) and each occurrence of each AE. The relationship should be classified as follows:

- **Not related**: Evidence exists that the AE has an etiology other than the study drug(s) (such as pre-existing condition, underlying disease, intercurrent illness, or concomitant medication)
- **Unlikely related:** a causal relationship between the study drug(s) and the AE is not a reasonable possibility
- **Possibly related:** The event has a suggestive temporal relationship to the study drug(s), and an alternative etiology is equally or less likely

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- **Related:** A temporal relationship exists between the event onset and administration of the study drug(s); it cannot be readily explained by the participant's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug; in case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge

An AE is considered causally related to the use of the study drug(s) when the causality assessment is either possibly related or related.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug(s) administration should be considered and investigated.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor; however, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

8.2.1.2 Adverse Event Severity Assessment

The severity of AEs will be graded as follows:

- **Mild**: An AE that is easily tolerated by the participant, causes minimal discomfort, does not interfere with everyday activities, and does not require intervention.
- **Moderate**: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe:** An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If an AE has multiple aspects, the aspect with the highest severity will be graded.

It is emphasized that the term severe is a measure of severity; thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but it may not be clinically serious.

In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., laboratory, X-ray, or ECG) should also be recorded as AEs. Test findings and physical examination findings can result in AEs if they:

- Are associated with accompanying symptoms, and/or
- Require additional diagnostic testing or medical/surgical intervention, and/or
- Lead to a change in study dosing or discontinuation from the study; result in the addition of significant additional concomitant drug treatment or other therapy, and/or
- Lead to any of the outcomes included in the definition of an SAE, and/or
- Are considered to be an AE by the Investigator or Sponsor.

Reporting as an AE should not be triggered by:

- Merely repeating an abnormal test, or

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- Any abnormal test result that is determined to be an error.

8.2.2 Serious Adverse Events

An SAE is any untoward medical occurrence that, on the basis of medical and scientific judgment:

- Results in death, or
- Is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), or
- Requires inpatient hospitalization for a medical reason or prolongation of existing hospitalization (this refers to hospital admission required for treatment of the AE). (Note: this does not include confinement in, for example, a respite unit; a skilled nursing unit; rehabilitation facility; the clinical site; or confinement due to planned or unplanned reason unrelated to study), or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other serious situations:

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

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 (including SAEs), regardless of relationship to the investigational product, will be collected and reported to the Sponsor until follow-up. SAEs that continue beyond the normal collection period (i.e., are ongoing at the time a participant exits the study) will be followed until resolution or until stabilized with sequelae. SAEs that begin after the participant's participation in the study is complete, but that the Investigator considers to be related to the study drug(s), may be reported at any time.

The Investigator or clinical site personnel must notify Drug Safety (Sponsor's designee) of all SAEs, regardless of relationship to the investigational drug(s), within 24 hours of clinical site personnel becoming aware of the event. The Investigator will provide the initial notification by sending a completed "SAE Notification Form," which must include the Investigator's assessment of the relationship of the event to the investigational drug and must be signed by the Investigator.

Follow-up information, or new information regarding an ongoing SAE, must be provided within 24 hours of knowledge by the study personnel to Drug Safety (Sponsor's designee).

All SAE reports should be sent to the contacts provided in the Investigator site file.

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8.2.3 Suspected Unexpected Serious Adverse Reactions

An SAE that is also an unexpected adverse drug reaction is called a suspected unexpected serious adverse reaction (SUSAR). Unexpected adverse reactions are adverse reactions of which the nature or severity is not consistent with the applicable product information (eg, IB for an unapproved investigational medicinal product or the United States Prescribing Information for an authorized medicinal product).

The Sponsor or its representative will promptly report (expedited reporting) the following SUSARs to applicable Health Authorities:

- SUSARs that have arisen in the current clinical study.
- SUSARs that have arisen in other clinical studies of the same Sponsor and with the same medicinal product.

Expedited reporting will occur no later than 15 calendar days after the Sponsor or its representative has first knowledge of the SUSAR. For fatal or life-threatening cases, reporting will occur at a maximum of 7 calendar days for a preliminary report with another 8 calendar days for completion of the report.

Investigators must also comply with local requirements for reporting SAEs and/or SUSARs to the local health authority and IRB as per local regulations.

8.2.4 Follow-up of Adverse Events

Follow-up of AEs will continue until resolution, stabilization, or death. In case of ongoing AEs at database lock, the data obtained at database lock will be used in the statistical analysis. The follow-up of the AE will be documented in the source documents and will be described in the final CSR only if considered relevant by the Investigator.

8.3 Pregnancy

A female clinical study participant must be instructed to stop taking the study drug and immediately inform the Investigator if she becomes pregnant during the study. Pregnancies occurring up to 30 days after the last dose of study drug(s) must also be reported to the Investigator. The Investigator will make arrangements for the participant to be counseled by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until the outcome of the pregnancy is known.

The Investigator should report all pregnancies of female clinical study participants to the Sponsor within 1 working day of becoming aware of them.

If the Investigator becomes aware of a pregnancy occurring in the partner of a male participant participating in the study up to 30 days after the last dose of study drug(s) of the male participant, the pregnancy should be reported to the Sponsor within 1 working day of obtaining written consent from the pregnant partner. The Investigator may make arrangements for the partner to be counseled by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the partner should continue until the outcome of the pregnancy is known.

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