Protocol J5B-MC-FHAD V2

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

NCT05994807

Approval Date: 11-Aug-2023

CLINICAL STUDY PROTOCOL

A PHASE 1, SINGLE-CENTER, OPEN-LABEL, 2-COHORT, FIXED--SEQUENCE, DRUG-DRUG INTERACTION STUDY TO ASSESS THE PHARMACOKINETICS OF DC-806 WHEN ORALLY ADMINISTERED ALONE, WHEN COADMINISTERED WITH ITRACONAZOLE, AND WHEN COADMINISTERED WITH CARBAMAZEPINE IN HEALTHY ADULT PARTICIPANTS

CONFIDENTIAL

Sponsor code: DCE806103

ICON code: SDITBEE42-0D1NX7

IND number: 163686

DC-806 Drug-Drug Interaction Study in Healthy Participants

Investigational product:	DC-806
Clinical phase:	Phase 1
Indication to be studied:	Not applicable

Sponsor:	DICE Therapeutics, Inc. 400 East Jamie Court, Suite 300 South San Francisco, CA 94080 United States
Contract Research Organization:	ICON Early Clinical Development Services 1255 East 3900 South Salt Lake City, UT 84124 United States
Principal Investigator:	PPD Medical Director - Early Phase Clinical Services Tel: PPD E-mail: PPD
Medical Monitor:	PPD Medical Director - Early Phase Clinical Services Tel: PPD E-mail: PPD

Version 2.0, 11 Aug 2023

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

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:

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REASON: I approve this document
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....

Sponsor Signatory:
PPD
VP, Clinical Development

11 Aug 2023
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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

PPD
Principal Investigator
Medical Director - Early Phase Clinical Services

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PPD

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).

SUMMARY OF CHANGES

The following changes have been introduced in Version 2.0 of the protocol (dated 11 Aug 2023).

Document	Date of Issue	Summary of Changes
Version 2.0	11 Aug 2023	The following changes were performed: • Change of Sponsor signatory to PPD VP Clinical Development. • Synopsis, Schedule of Assessments (SOAs) - The SOAs in Table 1 and Table 2 have been corrected to reflect that Day 2 electrocardiogram (ECG) is not required for any cohort. - In Table 1 and Table 2, correspondent footnotes "a" have been updated to clarify that on Day 11 (Cohort 1) and Day 25 (Cohort 2) the physical examinations are not mandatory and will only be symptom-driven, per Investigator's discretion. - In Table 1 and Table 2, correspondent footnotes "f" have been updated to include predose pharmacokinetic (PK) sample for DC-806 and CCI on Day 7 (Cohort 1) and Day 18 (Cohort 2). - In Table 2, the mark for blood sampling for pharmacogenomics was moved from Day -1 to Day 1 (predose) for Cohort 2, to mirror the SOA for Cohort 1, Table 1; correspondent footnote "g" was corrected for both Table 1 and Table 2. - Table 1 and Table 2 correspondent footnotes have been updated to include time windows for clinical laboratory tests, ECGs, vital signs, and PK sampling. • Section 3.3.1 Inclusion Criterion #7, and Section 3.4.8.2 Contraception: - The male contraception period has been updated to align with the Institutional Review Board (IRB) ICF review request to allow sperm donation or fathering a child to occur only after 90 days (instead of 30 days) after the last dose of study drug(s). • Section 3.4.5 Study Drug Administration - The specific time window for morning dosing was removed to alleviate operational challenges of accommodating large groups of subjects dosing schedules. • Section 8.3 Pregnancy - The period for females receiving itraconazole reporting pregnancies has been updated from "30 days" to "2 months" after the last dose of itraconazole. - The period for reporting pregnancies occurring in the partner of a male participant has been updated from "up to 30 days" to "up to 90 days" after the last dose of study drug of the male participant. - These changes were made to comply with the IRB ICF review request.
Original Protocol (Version 1.0)	08 Jun 2023	Not Applicable

SYNOPSIS

Study Title

A PHASE 1, SINGLE-CENTER, OPEN-LABEL, 2-COHORT, FIXED-SEQUENCE, DRUG-DRUG INTERACTION STUDY TO ASSESS THE PHARMACOKINETICS OF DC-806 WHEN ORALLY ADMINISTERED ALONE, WHEN COADMINISTERED WITH ITRACONAZOLE, AND WHEN COADMINISTERED WITH CARBAMAZEPINE IN HEALTHY ADULT PARTICIPANTS

Short Study Title

DC-806 Drug-Drug Interaction Study in Healthy Participants

Study Codes

Sponsor code : DCE806103
ICON code : SDITBEE42-0D1NX7
IND number : 163686

Sponsor

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Objectives and Endpoints

Objectives	Endpoints
Primary	Primary
• To assess the effect of a CYP3A4 inhibitor (itraconazole) and CYP3A4 inducer (carbamazepine) on the single dose PK of DC-806 coadministered with itraconazole or carbamazepine in healthy male and female participants	• Plasma PK parameters of DC-806: C_{max}, AUC_{0-t}, and AUC_{0-inf}, after dosed alone versus when coadministered with itraconazole or carbamazepine
Secondary	Secondary
• To evaluate the safety and tolerability of DC-806 in the absence and presence of a CYP3A4 inhibitor (itraconazole), and a CYP3A4 inducer (carbamazepine) in healthy male and female participants	• Incidence of AEs • Change from baseline in clinical laboratory, vital signs, physical examination findings, 12-lead ECG
Exploratory	Exploratory
CCI	

AE=adverse event; CYP=cytochrome P450; ECG=electrocardiogram; PK=pharmacokinetics

Design and Treatments

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

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

The following treatments will be administered:

Cohort 1 (n=CCI

Period 1: A single oral dose of CCI mg DC-806 on Day 1 under fasted conditions

Period 2: Multiple oral doses of once daily (QD) CCI mg itraconazole (CCI mg capsules) for 3 days (Day 4 to Day 6) under fed conditions

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

Cohort 2 (n=CCI

Period 1: A single oral dose of CCI mg DC-806 on Day 1 under fasted conditions

Period 2: Multiple-ascending oral doses of twice daily (BID) carbamazepine, under fed conditions, as follows:

- Day 4 to Day 5: BID doses of CCI mg carbamazepine
- Day 6 to Day 7: BID doses of CCI mg carbamazepine
- Day 8 to Day 17: BID doses of CCI mg carbamazepine (CCI mg + CCI mg tablets)

Period 3: On Day 18, morning dosing: a single oral dose of CCI mg DC-806 will be coadministered with CCI mg carbamazepine (CCI mg + CCI mg tablets) under fasted conditions.

Evening dosing: a single oral dose of CCI mg carbamazepine (CCI mg + CCI mg tablets) will be administered under fed conditions.

BID administration of CCI mg carbamazepine will continue until Day 20, followed by down-titration until Day 24:

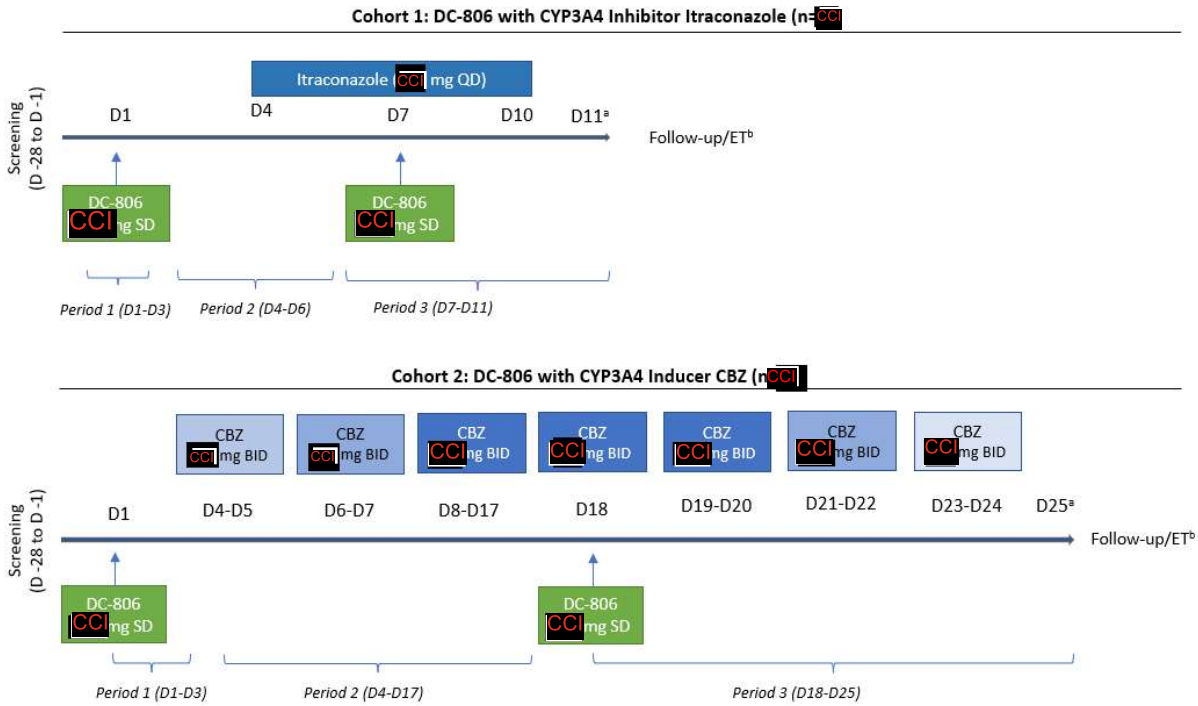
- Day 21 to Day 22: BID doses of CCI mg carbamazepine, under fed conditions
- Day 23 to Day 24: BID doses of CCI mg carbamazepine, under fed conditions

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

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

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

Figure 1 Study Schema



BID=twice daily (morning and evening); CBZ=carbamazepine; CYP=cytochrome P450; D=day; ET=early termination; n=number of participants;
SD=single dose; QD=once daily.
[a]Participants will be discharged on Day 11 (Cohort 1) and on Day 25 (Cohort 2), after completion of assessments;
[b]Follow-up: 10 (±2) days after the last dose of itraconazole (Cohort 1), and 6 (+2) days after the last dose of carbamazepine (Cohort 2), or at ET.

Study Schedule

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

Treatment period : **Cohort 1 (itraconazole, CYP3A4 inhibitor)**
Participants will be admitted to the clinical site on Day −1, which is the day prior to Day 1, the day of the first drug administration. Participants will be discharged on Day 11 after completion of all assessments.
Cohort 2 (carbamazepine, CYP3A4 inducer)
Participants will be admitted to the clinical site on Day −1, which is the day prior to Day 1, the day of the first drug administration. Participants will be discharged on Day 25 after completion of all assessments.

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

Participants

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

Main Criteria for Inclusion

Sex	: Male or female; females must be of non-childbearing 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 Medication

Active substance	: DC-806
Mechanism of action	: Inhibition of CCI
In development for	: Oral therapy for the treatment of psoriasis
Strength	: CCI mg
Dosage form	: Oral CCI
Manufacturer	: Patheon Pharmaceuticals Inc. (Thermo Fisher Scientific Inc.)

CYP inhibitor

Active substance	: Itraconazole
Mechanism of action	: Triazole antifungal agent (used as CYP3A4 inhibitor in Cohort 1)
Strength	: CCI mg
Dosage form	: Oral capsules
Manufacturer	: Sourced by pharmacy at ICON

CYP inducer

Substance	: Carbamazepine
Mechanism of action	: Antiepileptic, neurotropic and psychotropic agent (used as CYP3A4 inducer in Cohort 2)
Strength	: CCI mg, CCI mg
Dosage form	: Oral tablets
Manufacturer	: Sourced by pharmacy at ICON

Assessments

Safety	: Adverse events, clinical laboratory, vital signs, 12-lead electrocardiogram (ECG), physical examination
Pharmacokinetics	: Plasma concentrations of DC-806 Plasma PK parameters of DC-806: C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf}, CL/F, and V_z/F
Exploratory	: CCI

Statistical Methods

Sample size calculation	: A total of approximately 32 healthy male and female participants will be enrolled in the study with up to CCI to be enrolled in each cohort, aiming to have approximately CCI evaluable participants per cohort assuming a CCI % drop out. No formal sample size calculation was done, because the extent of the potential interaction effect is unknown. The sample size of 32 participants (up to CCI per cohort) has been determined adequate to meet the study objectives.
Safety	: Descriptive statistics for all relevant safety and tolerability parameters: adverse events, clinical laboratory data, vital signs, ECGs, and physical examination parameters, as well as any other parameter that is relevant for safety analysis.
Pharmacokinetics	: Descriptive statistics for all relevant PK parameters: n, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation; analysis of variance on C_{max} and area under the curve (AUC) to determine the size of any potential interaction(s).
Exploratory	: CCI [redacted]

Table 1 Schedule of Assessments – Cohort 1

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

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

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

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

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

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

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

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

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

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

Table 2 Schedule of Assessments – Cohort 2

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

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

[a] Complete physical examinations will be conducted at screening and follow-up/ET. Symptom-driven physical examinations will be conducted at any time, including at discharge, per the Investigator's discretion. The physical examination at discharge on Day 25 is not mandatory and will only be symptom-driven, based on the Investigator's discretion.

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

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

[d] Single 12-lead ECGs will be performed (after participant has rested at least 5 minutes in the supine position) at screening, Day -1, Day 18 (predose), Day 19 (predose) and at follow-up/ET. 12-lead ECGs will be performed in triplicate on Day 1 (predose and 1 hour postdose). Note: ECG time windows: predose within 1 hour prior to reference dosing; 1 hour postdose ±5 minutes

[e] Vital signs (supine systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate): at screening; on Day -1 (admission); at predose and at 1, 2, 6, and 24 hours postdose for DC-806; discharge (Day 25) and at follow-up/ET. Note: vital signs time windows: predose within 1 hour prior to reference dosing; 1 hour/2 hour/6 hour postdose ±5 minutes; 12 hour postdose ±10 minutes; 24 hour post dose ±60 minutes

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

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

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

TABLE OF CONTENTS

TITLE PAGE 1
SPONSOR AUTHORIZATION OF CLINICAL STUDY PROTOCOL 2
AUTHORIZATION OF CLINICAL STUDY PROTOCOL BY CONTRACT RESEARCH ORGANIZATION 3
SERIOUS ADVERSE EVENT CONTACT INFORMATION 4
SUMMARY OF CHANGES 5
SYNOPSIS 6
TABLE OF CONTENTS 16
TABLE OF TABLES 19
TABLE OF FIGURES 19
LIST OF ABBREVIATIONS 20
1. INTRODUCTION 22
1.1 Background 22
1.1.1 DC-806 22
1.1.2 Clinical Safety Data 22
1.1.3 Clinical Pharmacokinetics 23
1.2 Risk-benefit Assessment and Risk Mitigation 25
1.3 Study Rationale 27
2. OBJECTIVES AND ENDPOINTS 28
3. INVESTIGATIONAL PLAN 29
3.1 Overall Study Design and Plan 29
3.1.1 Type of Study 29
3.1.2 Screening Period 30
3.1.3 Treatment Period 30
3.1.4 Follow-up/Early Termination 31
3.1.5 Start and End of Study and Duration of the Study 31
3.2 Discussion of Study Design 31
3.2.1 Study Population 31
3.2.2 Type of Study 31
3.2.2.1 Cohort 1: Itraconazole as CYP3A4 and P-gp Inhibitor 32
3.2.2.2 Cohort 2: Carbamazepine as a CYP Inducer 32
3.2.2.3 PK Sampling 32
3.2.3 COVID-19 Risk Mitigation 32

3.2.4 Other ... 33
3.3 Selection of Study Population ... 33
3.3.1 Inclusion Criteria ... 33
3.3.2 Exclusion Criteria ... 34
3.3.3 Removal of Participants from the Study or Assessment ... 35
3.3.3.1 Stopping Rules for Individual Participants ... 36
3.4 Treatments ... 36
3.4.1 Treatments Administered ... 36
3.4.2 Identity of Investigational Product ... 37
3.4.3 Method of Assigning a Screening/Participant Number to Participants ... 38
3.4.4 Selection of Doses in the Study ... 38
3.4.5 Study Drug Administration ... 39
3.4.6 Meals During the Study ... 39
3.4.7 Blinding ... 39
3.4.8 Concomitant Medication and Other Restrictions During the Study ... 40
3.4.8.1 Concomitant Medication ... 40
3.4.8.2 Contraception ... 40
3.4.8.3 Other Restrictions ... 41
3.4.9 Treatment Compliance ... 41
3.5 Pharmacokinetic and Safety Assessments ... 41
3.5.1 Pharmacokinetic and Safety Assessments and Schedule of Assessments ... 41
3.5.1.1 Blood Sampling and Pharmacokinetic Assessments ... 41
3.5.1.1.1 Blood Sampling ... 41
3.5.1.2 Safety and Tolerability Monitoring ... 42
3.5.1.2.1 Adverse Event Collection and Reporting to the Sponsor ... 42
3.5.1.2.2 Clinical Laboratory Assessments ... 42
3.5.1.2.3 Vital Signs ... 43
3.5.1.2.4 Electrocardiogram ... 43
3.5.1.2.5 Physical Examination ... 43
3.5.1.2.6 Columbia-Suicide Severity Rating Scale ... 44
3.5.1.3 Pharmacogenomic Assessments ... 44
3.5.1.4 Total of Blood Volume ... 44
3.5.2 Appropriateness of Assessments ... 44
3.5.2.1 Timing of Assessments ... 44
3.5.3 Drug Concentration Measurements ... 44
3.5.4 Retention of Blood Samples ... 45
3.6 Statistical Procedures and Determination of Sample Size ... 45

3.6.1 Analysis Set 45
3.6.1.1 Safety Analysis Set 45
3.6.1.2 Pharmacokinetic Analysis Set 45
3.6.2 Statistical and Analytical Plan for Assessing Impact of Itraconazole and Carbamazepine on DC-806 Pharmacokinetics and Safety 45
3.6.2.1 Pharmacokinetic Evaluation 45
3.6.2.2 Evaluation of Safety and Tolerability 46
3.6.2.2.1 Adverse Events 46
3.6.2.2.2 Clinical Laboratory Data 46
3.6.2.2.3 Vital Sign, Electrocardiogram and Physical Examination Parameters 47
3.6.2.3 Exploratory Evaluation 47
3.6.3 Determination of Sample Size 47
3.7 Data Quality Assurance 47
4. ETHICS 48
4.1 Ethical Conduct of the Study 48
4.2 Institutional Review Board 48
4.3 Participant Information and Consent 49
4.4 Privacy 49
5. STUDY ADMINISTRATIVE STRUCTURE 50
5.1 Documentation 50
5.1.1 Archiving 50
5.1.2 Recording of Data in Source Documents and Electronic Case Report Forms 50
6. CONFIDENTIALITY AND PUBLICATION POLICY 51
7. REFERENCES 52
8. APPENDICES 54
8.1 Drug Accountability 54
8.2 Adverse Events and Serious Adverse Events Evaluation and Reporting 54
8.2.1 Adverse Events 54
8.2.1.1 Adverse Event Causality Assessment 54
8.2.1.2 Adverse Event Severity Assessment 55
8.2.2 Serious Adverse Events 55
8.2.3 Suspected Unexpected Serious Adverse Reactions 56
8.2.4 Follow-up of Adverse Events 57
8.3 Pregnancy 57

TABLE OF TABLES

Table 1 Schedule of Assessments – Cohort 1 12
Table 2 Schedule of Assessments – Cohort 2 14
Table 3 Pharmacokinetic Parameters 46

TABLE OF FIGURES

Figure 1 Study Schema 9
Figure 2 Study Schema 30

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CBZ	carbamazepine
CDER	Center for Drug Evaluation and Research
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
DRESS	Drug Rash and Eosinophilia and Systemic Symptoms
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
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
INR	international normalized ratio
IRB	Institutional Review Board
LDL	low density lipoprotein
LS	least-squares
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	single dose
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal

WMA	World Medical Association

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

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 of 0.09% to 11.4% across countries, 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.

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 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 an 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, 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), a total of 13 participants received 200 mg BID DC-806, 8 participants received 800 mg BID DC-806, and 11 participants received placebo BID for up to 28 days.

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 twice daily doses for up to 28 days in participants with psoriasis. There were no treatment-related discontinuations due to treatment-emergent adverse events (TEAEs), no 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 that were considered 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, mild 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 the 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]

1.1.3 Clinical Pharmacokinetics

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 t_{max} ranging from 0.75 to 1.75 hours postdose. DC-806 exposure increased with increasing DC-806 doses, with the highest 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 was observed after administration of 200 mg DC-806 with a high-fat, high-calorie meal. C_{max} and $AUC_{0-\infty}$ values were, respectively, 225 ng/mL and 755 ng·h/mL in the fed state, and 279 ng/mL and 857 ng·h/mL 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 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 (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 at steady state for BID regimens. Moderate intrasubject variability in exposure was observed 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 total dose administered. Renal clearance values were consistently low (2.43 L/h and 2.87 L/h at steady state) compared to apparent clearance of 134.8 L/h and 89.0 L/h in the 400 mg BID and 800 mg BID groups.

Following administration of 200 mg and 800 mg BID doses of DC-806 in participants with mild to moderate psoriasis for 28 days, DC-806 absorption was rapid and DC-806 exposure increased with increasing DC-806 doses; C_{max} values at steady state were 484 ng/mL in the 200 mg group and 2936 ng/mL in the 800 mg group. Steady state was reached within the first week of BID dosing. The mean trough concentration at 200 mg BID dose ranged from 19 to 47 ng/mL (~5× to 12× the half-maximal inhibitory concentration of CCI) and at 800 mg BID dose ranged from 182 to 220 ng/mL (~5× to 6.8× the 90% of maximal inhibitory concentration of CCI).

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 nonclinical program, including nonclinical PK and metabolism, clinical PD, and (exploratory) clinical efficacy are provided in the DC-806- IB.[1]

Itraconazole:

Absorption: Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral dose. The observed absolute bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.

Distribution: Most of the itraconazole in plasma is bound to protein (99.8%) with albumin being the main binding component (99.6% for the hydroxy-metabolite). It has also a marked affinity for lipids. Only 0.2% of the itraconazole in plasma is present as free drug. Itraconazole is distributed in a large apparent volume in the body (>700 L), suggesting its extensive distribution into tissues: concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be 2 to 3 times higher than corresponding concentrations in plasma. Brain to plasma ratios were about 1 as measured in beagle dogs. The uptake into keratinous tissues, skin in particular, is up to 4 times higher than in plasma.

Biotransformation: Itraconazole is extensively metabolized by the liver into a large number of metabolites. One of the main metabolites is hydroxy-itraconazole, which has in vitro antifungal activity comparable to itraconazole. Plasma concentrations of the hydroxy-itraconazole are about twice those of itraconazole. As shown in in vitro studies, cytochrome P450 (CYP)3A4 is the major enzyme that is involved in the metabolism of itraconazole.

Elimination: Itraconazole is excreted as inactive metabolites to about 35% in urine within one week and to about 54% with feces. Renal excretion of the parent drug accounts for less than 0.03% of the dose, whereas fecal excretion of unchanged drug varies between 3–18% of the dose. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

Linearity/non-linearity: As a consequence of non-linear PK, itraconazole accumulates in plasma during multiple dosing. Steady state concentrations are generally reached within about 15 days, with C_{max} and AUC values 4 to 7-fold higher than those seen after a single dose. The mean elimination half-life of itraconazole is about 40 hours after repeated dosing.[2]

Carbamazepine

Absorption: Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours following single oral doses. After a single oral dose of 400 mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approximately 4.5 µg/mL. Steady state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon autoinduction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

Distribution: Carbamazepine becomes bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in the saliva reflects the non-protein-bound portion present in the serum (20-30%).

Metabolism: Carbamazepine is catabolized into its primary pharmacologically active metabolite, carbamazepine-10,11 epoxide, which is then further metabolized primarily into carbamazepine 10,11-transdiol. A small portion of the carbamazepine-10,11 epoxide is also converted into 9-hydroxymethyl-10-carbamoyl-acridan. Additional biotransformation products include various monohydroxylated compounds and the N-glucuronide of carbamazepine produced by UGT2B7. The elimination half-life of unchanged carbamazepine in plasma averages approximately 36 hours following a single oral dose. Repeated administration leads to autoinduction of hepatic enzymes and an elimination half-life of only 16-24 hours, depending on the length of the treatment. In patients receiving concomitant treatment with other enzyme-inducing antiepileptic agents, half-life values averaging 9-10 hours have been found. The mean elimination half-life of carbamazepine-10,11 epoxide in the plasma is about 6 hours following single oral doses of the epoxide itself.

Excretion: Only 2-3% of carbamazepine, whether administered as a single or in repeated doses, is excreted in the urine in an unchanged form. Approximately 30% of carbamazepine is renally eliminated via the carbamazepine-10,11 epoxide pathway with carbamazepine 10,11-trans-diol as the main urinary metabolite.[3]

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-doses administration in adult healthy participants and participants with psoriasis. Differing doses of DC-806 will be used in the interaction study with itraconazole (CCI mg) or carbamazepine (CCI mg) to ensure that plasma levels of DC-806 would be expected to be safe in case of CYP3A4 inhibition, and still be measurable in case of CYP3A4 induction. The dose of CCI mg DC-806 used in Cohort 1 of the current study was selected in order to ensure that plasma levels would be expected to be safe in case of CYP3A4 inhibition. At the CCI mg single dose there will be CCI and CCI margin exposure for C_{max} and AUC, respectively when compared to the maximum observed exposure at CCI mg BID at steady state (Study DCE-806101). Using the net effect model[4] it is predicted that

itraconazole will have a potential CCI increase in the DC-806 exposure, which are well within these exposure margins.

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.

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 1 clinical study; nevertheless, ECGs will be monitored during this study.

The potential risks observed with DC-806 or other CCI occurring in this study are reduced, considering the selected single dose of CCI mg DC-806 for Cohort 1 and CCI mg DC-806 for Cohort 2 in this study (see Section 3.4.4 for dose selection), and study eligibility criteria. Also, participants will be carefully monitored after dosing.

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.

Itraconazole and carbamazepine are both registered drugs, and the safety and tolerability for both drugs are well known. See the full prescribing information for a detailed list of adverse reactions reported following the use of itraconazole and carbamazepine. The use of itraconazole and carbamazepine in this study is consistent with best practices for evaluating DDIs.

Although reported infrequently, blood dyscrasias (e.g., aplastic anemia, agranulocytosis) have been observed during the use of carbamazepine. However, adequate safety measures will be instituted, including assessments of all the hematological parameters throughout the duration of the study to mitigate this event.

Dermatological AEs also have been reported to occur with the use of carbamazepine. Drug Rash and Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome, and, rarely toxic epidermal necrolysis have been reported to occur as a result of exposure to carbamazepine. To mitigate this risk, continuous monitoring for any dermatological reaction such as skin rashes will be undertaken and investigated further if warranted.

Participants with HLA-B*1502 genotype have an increased risk of developing Stevens-Johnson Syndrome and toxic epidermal necrolysis after administration of carbamazepine. Since this genotype is almost exclusively observed in Asians, participants with Asian ancestry (including those who have 1 or more Asian grandparents) are excluded from participation in Cohort 2.

Antiepileptic drugs, including carbamazepine, increase the risk of suicidal thoughts or behavior. Therefore, participants with suicidal thoughts or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) during screening, will be excluded from Cohort 2.

Carbamazepine may affect the ability to drive and use machines, therefore, participants will be advised to exercise due caution when driving a vehicle or operating machinery. Additionally, a symptom-driven physical exam will be performed before discharge for Cohort 2, to mitigate this risk.

Cases of congestive heart failure, peripheral edema, pulmonary edema, and cardiac dysrhythmias have been reported with the use of itraconazole. To mitigate this risk, only healthy volunteers will be included, and they will be closely monitored throughout the study (e.g., ECG monitoring).

Itraconazole has also been associated with rare cases of serious hepatotoxicity, including liver failure and death. If clinical signs of hepatotoxicity develop, administration of itraconazole should be discontinued immediately and liver function testing performed. To mitigate the risk of hepatotoxicity, clinical labs will be performed at specific timepoints, and volunteers will be closely monitored.

1.3 Study Rationale

In view of the available nonclinical and clinical data, further development of DC-806 for the treatment of patients with psoriasis is warranted. DDI studies have an important role in drug development, with objectives being to determine whether potential interactions between an investigational drug and other drugs exist.[4] This study will provide an assessment of the safety, tolerability, and PK of DC-806 in the absence and presence of a CYP3A4 inhibitor (itraconazole) and a CYP3A4 inducer (carbamazepine) in healthy male and female participants.

DC-806 is a substrate of CYP3A4 and CYP3A4 was also identified as the primary isoform responsible for metabolism of DC-806. Hence when CYP3A4 was inhibited or induced by known perpetrators, it was anticipated to result in changes in systemic DC-806 exposure. The current study is designed to characterize the extent of these changes and potential impact on the safety profile of DC-806.

Itraconazole is a potent and widely used triazole antifungal agent and a prototypic, strong, and competitive inhibitor of CYP3A4, whereas carbamazepine is an anticonvulsant and specific analgesic for trigeminal neuralgia and is a strong inducer of CYP3A4. Both of these drugs are established by the Food and Drug Administration (FDA) to be used in DDI studies.[5] Itraconazole reduces the metabolism and increases the exposure of drugs metabolized by the CYP3A4 pathway, while carbamazepine enhances the metabolism and decreases the exposure of these drugs.
The rationale for dose selection and discussion of study design is described in Section 3.4.4.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	Primary
• To assess the effect of a CYP3A4 inhibitor (itraconazole) and CYP3A4 inducer (carbamazepine) on the single dose PK of DC-806 coadministered with itraconazole or carbamazepine in healthy male and female participants	• Plasma PK parameters of DC-806: C_{max}, AUC_{0-t}, and AUC_{0-inf}. after dosed alone versus when coadministered with itraconazole or carbamazepine
Secondary	Secondary
• To evaluate the safety and tolerability of DC-806 in the absence and presence of a CYP3A4 inhibitor (itraconazole) and a CYP3A4 inducer (carbamazepine) in healthy male and female participants	• Incidence of AEs • Change from baseline in clinical laboratory, vital signs, physical examination findings, 12-lead ECG
Exploratory	Exploratory
CCI	

AE=adverse event; CYP=cytochrome P450; ECG=electrocardiogram; PK=pharmacokinetics

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

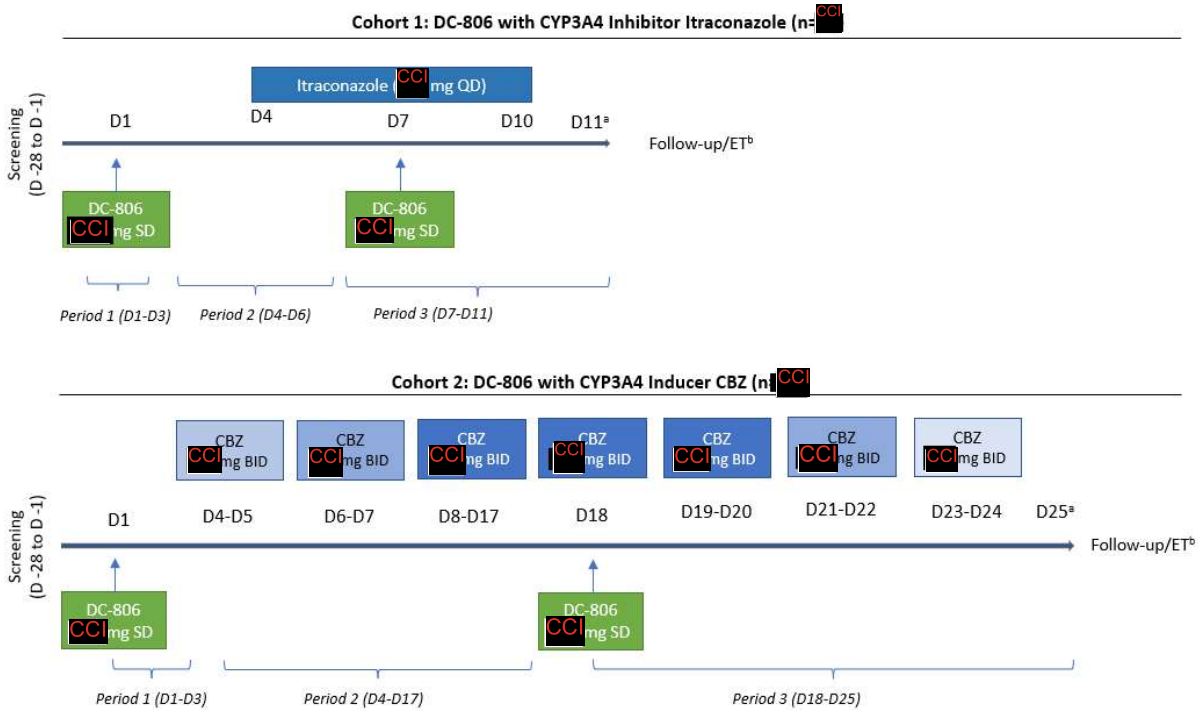
This study will consist of 2 cohorts with DC-806 serving as the victim drug in each cohort. Each study cohort will consist of 3 periods.

Cohort 1 - Study Treatment (itraconazole, CYP3A4 inhibitor): Participants will receive a single CCI mg dose of DC-806 alone under fasted conditions in Period 1. In Period 2, from Day 4 to Day 6, participants will receive multiple oral doses of once daily (QD) CCI mg itraconazole under fed conditions. On Day 7 (Period 3), a single oral dose of CCI mg DC-806 will be administered 2 hours after a single oral dose of CCI mg itraconazole under fasted conditions. QD dosing of itraconazole (CCI mg) will continue until Day 10 under fed conditions.

Cohort 2 - Study Treatment (carbamazepine, CYP3A4 inducer): Participants will receive a single CCI mg dose of DC-806 alone under fasted conditions in Period 1. In Period 2, from Day 4 to Day 17, participants will receive multiple-ascending doses of twice daily (BID) carbamazepine, under fed conditions, with CCI mg being the highest carbamazepine dose administered. On Day 18 (Period 3) a single oral dose of CCI mg DC-806 will be coadministered with the morning dose of CCI mg carbamazepine, under fasted conditions, followed by CCI mg carbamazepine alone as the evening dose, under fed conditions. BID administration of CCI mg carbamazepine will continue until Day 20, followed by down-titration until Day 24, under fed conditions.

A diagram of the study design is presented in Figure 2.

Figure 2 Study Schema



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

[a]Participants will be discharged on Day 11 (Cohort 1) and on Day 25 (Cohort 2), after completion of assessments;
[b]Follow-up: 10 (±2) days after the last dose of itraconazole (Cohort 1), and 6 (+2) days after the last dose of carbamazepine (Cohort 2), or at ET.

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

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 participants.

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 schedules of assessments (Table 1 or Table 2)

3.1.3 Treatment Period

Participants will be confined in the clinic for 3 treatment periods. Participants will be admitted to the clinical site on Day -1, which is the day prior to Day 1, the day of the first study drug administration.

They will be discharged on Day 11 (Cohort 1) and Day 25 (Cohort 2) (after the last dose of study drug) or at early termination, after completion of the assessments.

Assessments during the treatment periods will be performed as presented in the schedules of assessments (Table 1 or Table 2).

3.1.4 Follow-up/Early Termination

The follow-up/early termination assessments will be performed 10 (±2) days after the last dose of itraconazole (Cohort 1) and 6 (+2) days after the last dose of carbamazepine (Cohort 2), or at the time of early termination.

Assessments during follow-up/early termination will be performed as presented in the schedules of assessments (Table 1 or 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 he/she 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.

The total duration of the study from screening until follow-up for participants will be 49 (±2) days for Cohort 1 and 59 (+2) 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.

Individuals who have Asian ancestry (including those who have 1 or more Asian grandparents) will be excluded form Cohort 2 of this study due to the prevalence of the HLA-B*1502 allele in the Asian population, which has been associated with an increased risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Since carbamazepine is used to treat epilepsy and may present a risk of epilepsy re-occurrence when withdrawn, individuals with a history of epilepsy are excluded from Cohort 2. In addition, individuals who have suicidality risk as assessed by C-SSRS will also be excluded from Cohort 2 as carbamazepine may increase the risk of suicidal thoughts and behavior. Of note, the relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy.[3]

3.2.2 Type of Study

The fixed-sequence design was chosen to allow each participant to serve as his/her own control with respect to DC-806 PK characteristics with and without CYP3A4 inhibition (Cohort 1) or induction (Cohort 2).

The planned safety monitoring, clinical tolerability, and favorable nonclinical toxicity profile of DC-806 support administration of 2 single doses of DC-806 to healthy adult males and females of non-childbearing potential in the present study.

Conducting the study in healthy adult participants mitigates the potential confounding effects of the disease state and concomitant medications.

3.2.2.1 Cohort 1: Itraconazole as CYP3A4 and P-gp Inhibitor

Itraconazole is a strong CYP3A4 inhibitor recommended by the FDA for use in DDI studies.[4] Itraconazole is also a CYP3A4 substrate, and its half-life is approximately 20 hours, with steady state being reached after 1 to 2 weeks. CYP3A4 inhibition that reaches near maximal- effect is observed after as few as 3 days of dosing with itraconazole. Oral administration of CCI mg per day of itraconazole with a 3-day lead-in showed adequately strong CYP3A4 inhibition in several itraconazole DDI studies to detect a DDI.[6]

DC-806 will be administered 3 days after the start of itraconazole administration to ensure that a stable maximal inhibition of CYP3A4 is maintained during the entire DC-806 PK sampling period. Dosing with itraconazole will continue for another 4 days (7 days in total) so that the PK of DC-806 can be evaluated while exposure to itraconazole was maintained.

3.2.2.2 Cohort 2: Carbamazepine as a CYP Inducer

Carbamazepine will be used as the strong CYP3A4 inducer in this study, per FDA recommendation.[5] The dose titration regimen for carbamazepine used in this study is consistent with the drug label[3] and is commonly used in studies where evaluation of potential DDIs by enzyme induction is performed. Carbamazepine will be up-titrated followed by a maintenance dose regimen (CCI mg BID) in order to maximize potential enzyme induction effects.

Considering the half-life of carbamazepine of ~35 hours, steady state would be reached in about 175 hours or 7-8 days (i.e., after 5 half-lives, considering the study drug is given at regular intervals). Consequently, in the current study, carbamazepine CCI mg BID will be dosed from Day 8 to Day 17 before the second dose of DC-806 being coadministered.

3.2.2.3 PK Sampling

Plasma sampling will be performed to characterize the PK and CCI with and without the presence of a strong CYP3A4 inhibitor in Cohort 1, and a strong CYP3A4 inducer in Cohort 2.

3.2.3 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 COVID-19 precautions and procedures are described in the site-specific guidance documents. Any precautionary measures for COVID-19 risk mitigation will be put in place at the discretion of the site medical team based on current local COVID-19 conditions.

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.

3.2.4 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. Additionally, in animal studies itraconazole has shown reproduction toxicity and carbamazepine may cause fetal harm when administered to a pregnant female. To minimize any potential risks, females who are breastfeeding or of childbearing potential will be excluded from participation in this clinical study.

A sufficient number of healthy, adult participants will be enrolled, which will allow the objectives of the study to be met.

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

A total of 32 healthy male and female participants, up to [redacted] participants in each cohort, are planned to be enrolled in the study, to have approximately [redacted] evaluable participants per 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 non-childbearing 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, inclusive, at screening.
5. Status : healthy participants.
   Note: Healthy status as defined by the absence of evidence of any clinically significant, in the opinion of the Investigator, active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology, and urinalysis.
6. At screening, females must be of non-childbearing 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 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 90 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, C-SSRS (Cohort 2 only) and vital signs, as judged by the Investigator.
13. Willing and able to sign the ICF.

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:

<u>All participants:</u>

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 at 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 facility and until discharge in the study period.
9. Positive screen for hepatitis B surface antigen, 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.

Cohort 2 Only:

17. Individuals who have Asian ancestry (including those who have one or more Asian grandparents).
18. Presence of active suicidal ideation or positive suicide behavior using the "Baseline/Screening" version of the C-SSRS and with either of the following criteria:
    - History of a suicide attempt within the 5 years prior to the Screening Visit. Participants with a history of a suicide attempt more than 5 years ago should be evaluated by a mental healthcare professional (e.g., locally licensed psychiatrist, psychologist, or master's level therapist) before enrolling into the study.
    - Suicidal ideation in the past month prior to the Screening Visit as indicated by a positive response ("Yes") to either Question 4 or 5 of the "Baseline/Screening" version of the C-SSRS.
19. History of epilepsy.
20. Leukopenia (white blood cell count <LLN), neutropenia (neutrophil count <LLN), or thrombocytopenia (platelet count <LLN), at screening or admission (Day -1).

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.

If a participant is withdrawn from the study, the Sponsor 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 or not, after having received the first dose of study drug, will be considered an early termination participant. If a participant is withdrawn for a reason related to the study drug (DC-806), 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, 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 at least one dose of study drug 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 event (i.e., an SAE considered to have a causal-relationship to at least one of the study drugs).
- A drug-related severe adverse event (i.e., severe nonserious AEs considered to have a causal-relationship to at least one of the study drugs).
- 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

Period 1: A single oral dose of CCI mg DC-806 on Day 1 under fasted conditions

Period 2: Multiple oral doses of QD CCI mg itraconazole (CCI mg capsules) for 3 days (Day 4 to Day 6), under fed conditions

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

Cohort 2 (n=CCI

Period 1: A single oral dose of CCI mg DC-806 on Day 1 under fasted conditions

Period 2: Multiple-ascending oral doses of BID carbamazepine, under fed conditions, as follows:
- Day 4 to Day 5: BID doses of CCI mg carbamazepine
- Day 6 to Day 7: BID doses of CCI mg carbamazepine
- Day 8 to Day 17: BID doses of CCI mg carbamazepine (CCI mg + CCI mg tablets)

Period 3: On Day 18, morning dosing: a single oral dose of CCI mg DC-806 will be coadministered with CCI mg carbamazepine (CCI mg + CCI mg tablets) under fasted conditions.
Evening dosing: a single oral dose of CCI mg carbamazepine (CCI mg + CCI mg tablets) will be administered under fed conditions.
BID administration of CCI mg carbamazepine will continue until Day 20, followed by down-titration until Day 24:
- Day 21 to Day 22: BID doses of CCI mg carbamazepine, under fed conditions
- Day 23 to Day 24: BID doses of CCI mg carbamazepine, under fed conditions

The study drug will be swallowed together with 240 mL tap water with the participant in the upright position (see Section 3.4.5).

3.4.2 Identity of Investigational Product

Active Medication

Active substance	: DC-806
Mechanism of action	: CCI
In development for	: Oral therapy for the treatment of psoriasis
Strength	: CCI mg
Dosage form	: Oral CCI
Manufacturer	: Patheon Pharmaceuticals Inc. (Thermo Fisher Scientific Inc.)

CYP inhibitor

Active substance	: Itraconazole
Mechanism of action	: Triazole antifungal agent (used as CYP3A4 inhibitor in Cohort 1)
Strength	: CCI mg
Dosage form	: Oral capsules
Manufacturer	: Sourced by pharmacy at ICON

CYP inducer

Substance	: Carbamazepine
Mechanism of action	: Antiepileptic, neurotropic and psychotropic agent (used as CYP3A4 inducer in Cohort 2)
Strength	: CCI mg, CCI mg
Dosage form	: Oral tablets
Manufacturer	: Sourced by pharmacy at ICON

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

3.4.3 Method of Assigning a 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 the ICF, 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 study drug administration will be considered screening failures.

3.4.4 Selection of Doses in the Study

DC-806

Differing doses of DC-806 will be used in the interaction study with itraconazole or carbamazepine to ensure that plasma levels would be expected to be safe in case of CYP3A4 inhibition and still be measurable in case of CYP3A4 induction. DC-806 at doses up to CCI mg BID was generally well tolerated following single- and multiple-doses administration in adult healthy participants and participants with psoriasis. The dose of CCI mg DC-806 used in Cohort 1 of the current study was selected in order to ensure that plasma DC-806 exposure would be expected to be safe in case of CYP3A4 inhibition. At the CCI mg single dose there will be CCI and CCI margin exposure for C_{max} and AUC, respectively when compared to the maximum observed exposure in healthy participants receiving CCI mg BID at steady state (DCE-806101). Using the net effect model[4] it is predicted that itraconazole will have a potential CCI increase in the DC-806 exposure, which are well within these exposure margins. Together, the nonclinical toxicology profile of DC-806 and clinical data collected to date for DC-806 support the proposed dose in present study.

Itraconazole

Itraconazole is a strong clinical index inhibitor of CYP3A4. The oral dose of CCI mg itraconazole, QD, is within the dosing range approved for therapeutic use and commonly used in studies evaluating potential DDI with itraconazole and has been shown to be safe and well tolerated in healthy participants.[2,6] Oral administration of CCI mg per day of itraconazole with a 3-day lead-in showed adequately strong CYP3A4 inhibition in several itraconazole DDI studies to detect a DDI.[6]

DC-806 will be administered 3 days after the start of itraconazole administration to ensure that a stable maximal inhibition of CYP3A4 is maintained during the entire DC-806 PK sampling period. Dosing with itraconazole will continue for another 4 days (7 days in total) so that the PK of DC-806 can be evaluated while exposure to itraconazole was maintained.

Carbamazepine

The dose titration regimen for carbamazepine used in this study is consistent with the drug label[3] and is commonly used in studies where evaluation of potential DDIs by enzyme induction is performed. Carbamazepine will be up-titrated followed by a maintenance dose regimen (CCI mg BID) in order to maximize potential enzyme induction effects. Considering the half-life of carbamazepine of ~35 hours, steady state would be reached in about 175 hours or 7-8 days (i.e., after 5 half-lives, considering the study drug is given at regular intervals). Consequently, in the current study, carbamazepine CCI mg BID will be dosed from Day 8 to Day 17 before the second dose of DC-806 being coadministered.

3.4.5 Study Drug Administration

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

Study drugs will be administered to participants in the morning after an overnight fast of at least 10 hours. As BID dosing is to be employed in Cohort 2, carbamazepine doses will be administered on an approximately every 12 hours schedule (±30 minutes).

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

Cohort 1:

The study drug DC-806 will be administered to participants in the morning on Day 1 and Day 7, after an overnight fast of at least 10 hours following standard dinner on the evening before. On Day 7 the study drug DC-806 will be administered 2 hours after itraconazole dosing. Fasting will continue for a period of at least 4 hours after administration of DC-806, i.e., until scheduled lunch. On other dosing days, fasting will continue for a period of at least 1 hour after itraconazole administration. 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.

On Day 1 and Day 7, participants will not lie down for 4 hours after drug administration, except when required for assessments that need to be performed.

Cohort 2:

On Day 1 and for the morning dosing of Day 18, study drug DC-806 will be administered to participants in the morning after an overnight fast of at least 10 hours following standard dinner the evening before. Fasting will continue for a period of at least 4 hours after administration of DC-806, 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.

On other dosing days (including evening dosing on Day 17), there will be no fasting requirements.

On Day 1 and in the morning dosing of Day 18, participants will not lie down for 4 hours after drug administration, except when required for assessments that need to be performed.

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 3.4.5, there are no special requirements related to food and beverage intake. When not fasting, meals and snacks (such as decaffeinated coffee, herbal tea, fruit, and 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 paracetamol: from admission onward, the Investigator may permit a limited amount of paracetamol 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.

Examples of prohibited medications include erythromycin, ciprofloxacin, monoamine oxidase inhibitors (e.g., selegiline), methadone, ergot alkaloids, etc. For a complete list, please see the product insert for carbamazepine and itraconazole.

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 90 days after 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 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
- 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.

Participants in same-sex relationships are not required to use contraception to prevent pregnancy.

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 ≥90 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, and energy drinks), and grapefruit (juice) and tobacco products are 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).

Participants will be advised to exercise due caution when driving a vehicle or operating machinery (Cohort 2 only).

3.4.9 Treatment Compliance

Study drug 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 and Safety Assessments

3.5.1 Pharmacokinetic and Safety Assessments and Schedule of Assessments

A schedule of assessments is presented in Table 1 and Table 2.

3.5.1.1 Blood Sampling and Pharmacokinetic Assessments

3.5.1.1.1 Blood Sampling

At the time points defined in the schedules of assessments, blood samples will be taken for the analysis of DC-806 and CCI [redacted] (as applicable) concentrations in plasma samples.

The blood samples will be taken via an indwelling intravenous (iv) catheter or by direct venipuncture. The exact times of blood sampling will be recorded in the eCRF.

Plasma samples may (in the future) also be used for research purposes such as CCI [redacted].

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 Event Collection and Reporting to the Sponsor

After informed consent has been obtained but before initiation of study drug, 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 drug, 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 or any event already present that worsens in either severity or frequency following exposure to the study drug.

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 drug 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.

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:

- 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, glucose (fasting), 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), low density lipoprotein (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.

- 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, methadone, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, 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.

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 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.

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 C-SSRS at screening in Cohort 2 of the study.

The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period.[7,8] 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.

3.5.1.3 Pharmacogenomic Assessments

At the time points defined in the schedules of assessments, a blood sample will be collected for CCI [redacted] The collection of this blood sample is optional for all participants and participant consent will be obtained prior to sample collection; participants who do not consent to collection of this sample will not be excluded from participation in this study provided all other inclusion and exclusion criteria have been met. The blood sample will be double coded (1 code at ICON and 1 code at the Sponsor), and the sample will be kept until 15 years after completion of the study.

The blood sample will be taken via an indwelling intravenous catheter or by direct venipuncture. The exact time of blood sampling will be recorded in the eCRF. Details on sample processing, storage, and shipping will be described in the laboratory manual prepared by ICON.

3.5.1.4 Total of Blood Volume

The total volume of blood drawn for a participant will not surpass 500 mL (except when extra blood samples need to be taken for safety reasons).

3.5.2 Appropriateness of Assessments

The assessments that will be made in this study are standard 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.

3.5.3 Drug Concentration Measurements

The analysis of DC-806 and CCI [redacted] (as applicable) in plasma samples will be performed using validated liquid chromatography-mass spectrometry/mass spectrometry method(s).

The bioanalytical report(s) for the determinations will be included in the clinical study report (CSR) as an appendix.

3.5.4 Retention of Blood 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 and CCI profiling 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 CCI. The samples will be stored for a maximum period of 5 years, after which the samples will be destroyed.

The blood sample for CCI will be stored for a maximum period of 15 years after completion of the study, after which the sample will be destroyed.

3.6 Statistical Procedures and Determination of Sample Size

3.6.1 Analysis Set

3.6.1.1 Safety Analysis Set

All participants who have received at least 1 dose of DC-806, itraconazole, or carbamazepine.

3.6.1.2 Pharmacokinetic Analysis Set

All participants who have received at least 1 dose of DC-806, itraconazole, or carbamazepine and provided sufficient bioanalytical assessment results to calculate reliable estimates of the DC-806 PK parameters.

3.6.2 Statistical and Analytical Plan for Assessing Impact of Itraconazole and Carbamazepine on DC-806 Pharmacokinetics and Safety

Descriptive statistics will be used for all relevant PK parameters: n, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation; analysis of variance on C_{max} and AUC to determine the size of any potential interaction(s).

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

A 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 DC-806 and CCI. The PK parameters to be determined or calculated using noncompartmental analysis from the plasma concentration-time data for DC-806 and CCI (as applicable) include, but are not

limited to, the parameters as given in Table 3. A complete list of PK parameters will be provided in the SAP.

Table 3 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 (λ_z)
$t_{1/2}$	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

The PK parameters and their statistical evaluation will be included in the CSR for this study. 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

A listing of all individual AEs will be provided. Summary tables of TEAEs will be presented by system organ class based on the MedDRA terminology list (preferred terms) including 1 table containing the number of TEAEs (frequency of occurrence, number of participants experiencing the event) by severity, relationship to the study drug, SAEs, and TEAEs leading to discontinuation, and 1 table containing the number of drug-related TEAEs (frequency of occurrence, number of participants experiencing the event). Additional tables of total counts by treatment and relationship and by treatment and severity will be given.

3.6.2.2.2 Clinical Laboratory Data

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 Sign, 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] may be evaluated.

3.6.3 Determination of Sample Size

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

3.7 Data Quality Assurance

The study may be audited by the Quality Assurance Department at ICON to assess adherence to the clinical study protocol 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.

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.

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.[9]

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)[10] 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 protocol 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 protocol and the ICFs will be submitted for review and approval by an IRB prior to the initiation of eligibility screening. The composition of the IRB will be in accordance with the recommendations of the ICH E6(R2) Guideline for Good Clinical Practice (GCP).[10]

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 taking part in the study.

4.3 Participant Information and Consent

All participants will be informed verbally and in writing regarding the objectives, procedures, risks of study participation, and about the optional collection of blood samples for pharmacogenomic assessments. 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.[11]

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.

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.

7. REFERENCES

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5. U.S. Food & Drug Administration. Drug Development and Drug Interaction | Table of Substrates, Inhibitors and Inducers. August 2022. Link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers Accessed at: 10 April 2023.
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10. 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. Adopted by the European Medicines Agency (EMA), Committee for Human Medicinal Products, Document Reference EMA/CHMP/ICH/135/1995), 14 Jun 2017.
11. Health Insurance Portability and Accountability Act of 1996. Public Law 104 191, 104th Congress.
12. 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. Note for Guidance on Clinical

Safety Data Management, Adopted by the Committee for Human Medicinal Products, European Medicines Agency (EMA), Document Reference CPMP/ICH/377/95, Jun 1995.

8. APPENDICES

8.1 Drug Accountability

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Accountability Forms) and disposition (e.g., 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).[12]

All AEs reported by the participants or apparent from their physical appearance after initiation of the study drug 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 (such as pre-existing condition, underlying disease, intercurrent illness, or concomitant medication)
- **Unlikely related:** a causal relationship between the study drug and the AE is not a reasonable possibility
- **Possibly related:** The event has a suggestive temporal relationship to the study drug, and an alternative etiology is equally or less likely
- **Related:** A temporal relationship exists between the event onset and administration of the study drug; 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 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
- 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, or
- 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 drug(s), only SAEs caused by a protocol-mandated intervention should be collected and reported to the Sponsor. After initiation of study drug(s), all AEs (including SAEs), regardless of relationship to the study drug(s), will be collected and reported to the Sponsor until follow-up. SAEs that are related to the study drug(s) and 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 study 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 study drug(s) 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.

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 (e.g., 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 the 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 serious adverse events 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 and/or Sponsor.

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 2 months after the last dose of study drug 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 90 days after the last dose of study drug 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.