Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

OPC-167832

REVISED CLINICAL PROTOCOL

A Phase 1, Single-center, Two-part, Open-label, Pharmacokinetic Trial to Assess the Potential for Cytochrome P450 3A Mediated Drug-drug Interactions with Orally Administered OPC-167832 Tablets in Healthy Adult Subjects

A Study to Test the Effects of Itraconazole and Carbamazepine on OPC-167832 in Healthy Men and Women

Protocol No. 323-201-00007
IND No. 129303

CONFIDENTIAL — PROPRIETARY INFORMATION

Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc.
Immediately Reportable Event	CCI [redacted] 3482
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CCI

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
Anti-HCV	Hepatitis C antibodies
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
BID	Twice a day
BMI	Body mass index
CBZ	Carbamazepine
CFR	Code of Federal Regulations
CFU	Colony-forming-unit
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Science
CL/F	Apparent clearance of drug from plasma after extravascular administration
C_{max}	Maximum (peak) plasma concentration of the drug
CRF	Case report form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
CYP1A1	Cytochrome P450 1A1
CYP2C19	Cytochrome P450 2C19
CYP3A	Cytochrome P450 3A
DAIDS	Division of AIDS
DDI	Drug-drug interaction
DS	Drug-susceptible
DS-TB	Drug-susceptible tuberculosis
ECG	Electrocardiogram
eCRF	Electronic case report form
eICF	Electronic informed consent form
ET	Early termination
FDA	Food and Drug Administration
FOCBP	Females of childbearing potential
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric mean ratio
h	Hours
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC50	Fifty percent inhibitory concentration

Abbreviation	Definition
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional review board
IRE	Immediately reportable event
ITC	Itraconazole
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Noninvestigational medicinal product
CCI	[redacted]
PK	Pharmacokinetic
PQC	Product quality complaint
q12h	Every 12 hours
QD	Once daily
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SoA	Schedule of assessments
$t_{1/2,z}$	Terminal-phase elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) plasma concentration
ULN	Upper limit of normal
US or USA	United States or United States of America
USPI	United States Prescribing Information
WBC	White blood cell

1 Protocol Summary

1.1 Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Investigational Medicinal Product: OPC-167832

Protocol No.: 323-201-00007

IND No.: 129303

Protocol Title: A Phase 1, Single-center, Two-part, Open-label, Pharmacokinetic Trial to Assess the Potential for Cytochrome P450 3A Mediated Drug-drug Interactions with Orally Administered OPC-167832 Tablets in Healthy Adult Subjects

Protocol Lay Person Short Title: A Study to Test the Effects of Itraconazole and Carbamazepine on OPC-167832 in Healthy Men and Women

Clinical Phase: 1

Planned Treatment/Indication: Tuberculosis

Objectives and Endpoints:

Objectives	Endpoints
Primary: To assess the potential for CYP-mediated drug-drug interactions with OPC-167832: • Inhibition of OPC-167832 metabolism via CYP3A by itraconazole • Induction of OPC-167832 metabolism via CYP3A by carbamazepine	Primary: OPC-167832 PK: C_{max}, AUC_t, and AUC_∞
Secondary: To assess the safety and tolerability of OPC-167832 administered alone or in combination with itraconazole or carbamazepine	Secondary: Safety: AEs, clinical laboratory tests, vital signs, physical examinations, 12-lead ECGs, and C-SSRS (Part 2 only)

AE = adverse event; AUC_∞ = area under the concentration-time curve from time zero to infinity; AUC_t = area under the concentration-time curve calculated to the last observable concentration at time t; C_{max} = maximum (peak) plasma concentration of the drug; C-SSRS = Columbia-Suicide Severity Rating Scale; CYP = cytochrome P450; ECG = electrocardiogram; PK = pharmacokinetics.

Trial Design: This is a single-center, 2-part, open-label drug-drug interaction (DDI) trial in healthy adult subjects. Part 1 and Part 2 will have fixed sequence designs with 12 subjects in each part for a total of 24 subjects enrolled.

Following a screening period of up to 28 days, eligible subjects will enter the clinic on the day prior to the first treatment day (Day −1).

For Part 1, the impact of CYP3A inhibition on the PK of OPC-167832 will be assessed. Subjects will receive a single, 30-mg, oral dose of OPC-167832 [redacted] in the fasted state on Day 1 with blood collections for PK assessment of OPC-167832 from Day 1 through Day 8. On Day 8, subjects will receive 200-mg doses of itraconazole in the morning and evening (200 mg twice daily [BID]) followed by 200 mg of itraconazole administered once daily on Day 9 through Day 14 to approach steady-state conditions for itraconazole. On Day 15, a single, 30-mg, oral dose of OPC-167832 [redacted] will be administered concurrently with a 200-mg dose of itraconazole in the fasted state with blood collections for PK assessment of OPC-167832 from Day 15 through Day 26. Once daily 200-mg doses of itraconazole will continue to be administered on Day 16 through Day 25. Subjects will be discharged from the clinic after the PK sample on Day 26 or early termination (ET).

For Part 2, the impact of CYP3A induction on the PK of OPC-167832 will be assessed. Subjects will receive a single, 30-mg, oral dose of OPC-167832 [redacted] on Day 1 in the fasted state with blood collections for PK assessment of OPC-167832 from Day 1 through Day 8. On Day 8 through Day 10, subjects will receive 100 mg BID carbamazepine followed by 200 mg BID carbamazepine administration on Day 11 through Day 13 and 300 mg BID carbamazepine administration on Day 14 through Day 31. On Day 25, a 30-mg oral dose of OPC-167832 [redacted] will be administered concurrently with the morning 300-mg dose of carbamazepine in the fasted state with blood collections for PK assessment of OPC-167832 from Day 25 through Day 32. Subjects will be discharged from the clinic after the PK sample on Day 32 or ET.

All subjects will be contacted by phone 30 days after the last dose of OPC-167832 to assess any new or ongoing AEs and to record concomitant medications.

Trial Population: Twenty-four subjects will be enrolled, 12 subjects in each part, such that approximately 10 healthy male or female subjects complete each part.

Key Inclusion/Exclusion Criteria: Male and female subjects between the ages of 18 and 55 years (inclusive), with a body mass index (BMI) between 19 and 32 kg/m^2 (inclusive), who are in good health as determined by medical history, physical examination, 12-lead electrocardiogram (ECG), serum/urine chemistry, hematology, and serology tests, and who are able to provide informed consent will be considered for inclusion in the trial.

Trial Site(s): This trial will be conducted at 1 site in the United States.

Trial Intervention(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration: OPC-167832, itraconazole, and carbamazepine will be administered orally to subjects as per the dosing schedule below. OPC-167832 CCI [redacted] will be provided as 30-mg tablets, itraconazole will be administered as a 10-mg/mL oral solution, carbamazepine will be administered as the least number of tablets based on commercially available extended-release tablets (ie, 100-mg tablet, 200-mg tablet). Lower dose strengths of carbamazepine can be combined, ie, a 100-mg tablet and a 200-mg tablet should be combined to dose at 300 mg. All doses will be administered with approximately 240 mL of room temperature, still water. When itraconazole is administered, some of the 240 mL of water should be used to rinse the dosing container. All doses of OPC-167832 (administered on Days 1 and 15 in Part 1 and Days 1 and 25 in Part 2) will be administered following an overnight fast of at least 10 hours.

For Part 1, OPC-167832 and itraconazole will be administered in the morning at the same time each day. The BID dose of itraconazole on Day 8 will be administered every 12 hours (q12h). On days of serial PK sampling days (Days 1 and 15), subjects will be required to continue to fast from food for at least 4 hours following dosing of OPC-167832 and water will be restricted for 1 hour before to 2 hours after dosing of OPC-167832. Water is permitted ad libitum on all other days.

For Part 2, OPC-167832 and carbamazepine will be administered in the mornings at the same time each day and BID doses of carbamazepine will be administered q12h and at same time each evening. On days of serial PK sampling days (Days 1 and 25), subjects will be required to continue to fast from food for at least 4 hours following of OPC-167832 and water will be restricted for 1 hour before to 2 hours after dosing of OPC-167832. Water is permitted ad libitum on all other days.

Study Day	Time	Dose
PART 1		
1	morning	30 mg OPC-167832
8	morning	200 mg itraconazole
	evening	200 mg itraconazole
9 through 14	morning	Once-daily 200 mg itraconazole
15	morning	30 mg OPC-167832 and 200 mg itraconazole
16 through 25	morning	Once-daily 200 mg itraconazole
PART 2		
1	morning	30 mg OPC-167832
8 through 10	morning	100 mg carbamazepine extended release
	evening	100 mg carbamazepine extended release
11 through 13	morning	200 mg carbamazepine extended release
	evening	200 mg carbamazepine extended release
14 through 24	morning	300 mg carbamazepine extended release[a]

Study Day	Time	Dose
	evening	300 mg carbamazepine extended release[a]
25	morning	30 mg OPC-167832 and 300 mg carbamazepine extended release[a]
	evening	300 mg carbamazepine extended release[a]
26 through 31	morning	300 mg carbamazepine extended release[a]
	evening	300 mg carbamazepine extended release[a]

[a]Lower dose strengths of carbamazepine can be combined, ie, a 100-mg tablet and a 200-mg tablet should be combined to dose at 300 mg.

Trial Assessments: Assessments for Pharmacokinetics: blood sampling to determine the concentrations of OPC-167832, itraconazole, and carbamazepine.

CCI [redacted]

Assessments for Safety: adverse events, clinical laboratory tests, 12-lead ECG, vital signs, physical examination findings, the Columbia-Suicide Severity Rating Scale (Part 2 only).

Screening/Other: Demographics, medical and medication history, serum hepatitis and human immunodeficiency virus screen, urine alcohol test, drug screen, severe acute respiratory syndrome coronavirus test, urine (and confirmatory serum, if needed) pregnancy test (for females of childbearing potential), follicle-stimulating hormone test (for postmenopausal females), and height/weight/BMI.

Independent Data Monitoring Committee: No

Statistical Methods: The trial plans to enroll 12 subjects in each treatment part to target approximately 10 completers per part. Sample size was selected assuming an intra-subject coefficient of variation for AUC of 25%, such that the point estimate of the ratio of geometric means for the PK parameters of OPC-167832 with and without coadministration of the perpetrator (itraconazole or carbamazepine) will fall within 83% and 120% of the true value with 90% confidence.

The effect of itraconazole or carbamazepine administration on the single-dose PK of OPC-167832 will be assessed using the primary PK parameters of OPC-167382: C_{max}, AUC_t, and AUC_∞ in the presence and absence of either itraconazole or carbamazepine.

Statistical analyses will be performed using the log-transformed PK parameters. The magnitude of the DDI will be assessed by computing the ratio of the geometric means of the OPC-167832 + potentially interacting drug versus OPC-167832 alone and the corresponding 90% confidence intervals (CIs) based on the log-transformed data.

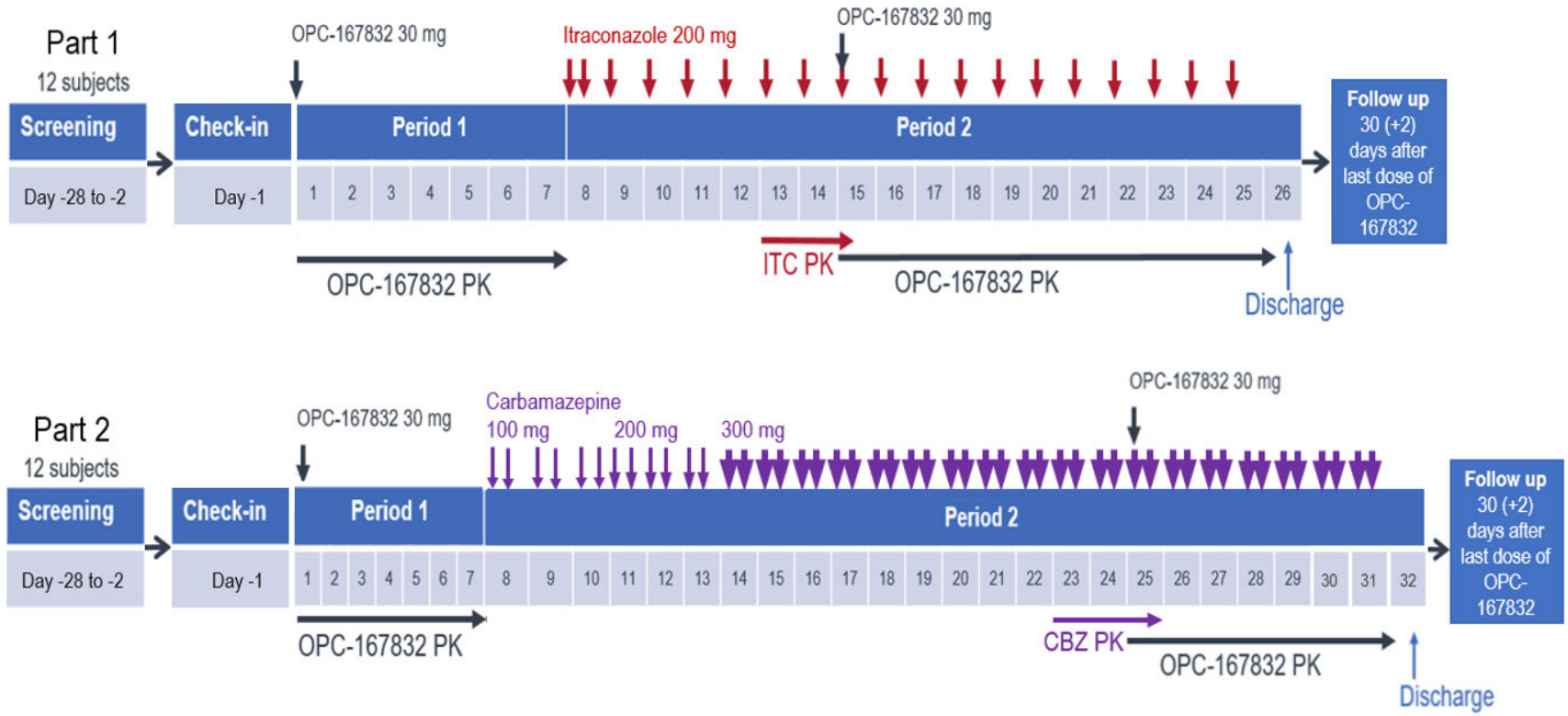
An analysis of variance will be performed on the log-transformed PK parameters C_{max}, AUC_t, and AUC_∞ for OPC-167832 and/or its metabolites using the MIXED procedure in SAS for each part separately. The mixed-effects linear model for each PK parameter will include treatment (OPC-167832 + potentially interacting drug [test] and OPC-167832 alone [reference]) as a fixed effect and subject as a random effect. From each analysis, mean differences between the treatments OPC-167832 + potentially interacting drug and OPC-167832 alone and the 90% CI for the differences will be derived. The antilog of the differences will then provide an estimate of the geometric mean ratios (GMR; OPC-167832 + potentially interacting drug/OPC-167832 alone), and the antilog of the confidence limits will provide the 90% CIs for the GMRs.

Trial Duration: Each subject in this trial is expected to participate in the following periods of the trial (approximate durations listed):

- Eligibility screening period: Day −28 to Day −2
- In-clinic treatment (2 dosing periods):
  - Part 1: Day −1 to Day 26 days (27 days)
    OR
  - Part 2: Day −1 to Day 32 (33 days)
- Safety follow-up phone call: 30 (+ 2) days after the last dose of OPC-167832 (eg, Day 45 [+ 2 days] for Part 1 and Day 55 [+ 2 days] for Part 2 for trial completers).

The trial start is defined as the date the first subject signs their informed consent form. Overall, the trial duration, from signing of the first subject's informed consent form to the last subject's final assessment, is expected to be approximately 11 weeks for Part 1 and approximately 12 weeks for Part 2.

1.2 Schema



CBZ = carbamazepine; ITC = itraconazole.

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments - Part 1

Period	Screening		Treatment											Follow-up Phone Call 30 (+2) days after last dose of OPC-167832	Notes
Visit	Screening	Check-in	Period 1			Period 2									
Trial Day	−28 to −2	−1	1	2	3 to 7	8	9 to 12	13	14	15	16	17 to 25	26 End-of-Trial or ET		
ENTRANCE/HISTORY															
Informed Consent	X														Section 10.1.2
Demographics	X														Section 5.1
Inclusion/Exclusion Criteria	X	X													Section 5.2
Medical History	X														
Height	X														Section 8.5.2
Body Weight	X	X											X		Section 8.5.2
Body Mass Index	X	X													Section 8.5.2
Serology (HIV, HBsAg, anti-HCV)	X														Section 10.2
Urine alcohol and urine drug screen	X	X													Section 10.2
Urine pregnancy test (for FOCBP)	X	X											X		Section 10.3
FSH (for postmenopausal females)	X														Section 10.2
TRIAL RESIDENCY															
Check-in to trial site clinic		X													
Discharge from Clinic													X		
SAFETY															
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.6.1
Physical Examination[a]	X	X								X			X		Section 8.5.2

Table 1.3-1 Schedule of Assessments - Part 1

Period	Screening		Treatment											Follow-up Phone Call 30 (+2) days after last dose of OPC-167832	Notes
Visit	Screening	Check-in	Period 1			Period 2									
Trial Day	−28 to −2	−1	1	2	3 to 7	8	9 to 12	13	14	15	16	17 to 25	26 End-of-Trial or ET		
Vital Signs[b]	X	X	X	X						X	X		X		Section 8.5.3
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
12-Lead ECG[c]	X	X	X	X						X	X		X		Section 8.5.4
Laboratory Tests (hematology, serum chemistry, and urinalysis [with cell count])	X	X	X	X						X	X		X		Section 8.5.1
IMP ADMINISTRATION															
OPC-167832			X							X					Section 6.1
Itraconazole[d]						X	X	X	X	X	X	X			Section 6.1
PHARMACOKINETICS															
Blood Samples for OPC-167832 PK[e]			X	X	X	X				X	X	X	X		Section 8.2.1
Blood Samples for Itraconazole PK[f]								X	X	X					Section 8.2.1
OTHER PROCEDURES															
CCI [redacted]															
Medication Compliance Evaluation			X			X	X	X	X	X	X	X			Section 6.4

anti-HCV = hepatitis C antibodies; FOCBP = females of childbearing potential; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus antibodies; .

[a] Complete physical examinations will be performed at screening, predose on Day 15, and prior to discharge or at ET. A targeted physical examination will be completed at check-in and at any time per the investigator's discretion.

[b]Vital signs will be measured at screening, on Day −1, predose on Day 1 and Day 15, 24 hours after OPC-167832 administration (Day 2 and Day 16), and prior to discharge on Day 26 or at ET.

[c]Twelve-lead ECGs will be performed at screening, on Day −1, predose on Day 1, 3 hours after OPC-167832 administration on Day 1, and 24 hours (Day 2) after OPC-167832 administration on Day 1, predose Day 15, 3 hours after OPC-167832 administration on Day 15, and 24 hours (Day 16) after OPC-167832 administration on Day 15, and prior to discharge on Day 26 or at ET.

[d]Subjects will receive 200 mg itraconazole in the morning and evening on Day 8 and 200 mg itraconazole in the morning on Day 9 through Day 25.

[e]Blood samples for OPC-167832 PK will be collected predose Day 1 and at 1, 2, 3, 4, 8, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 168 (Day 8) hours postdose; predose Day 15 and at 1, 2, 3, 4, 8, 12, 24 (Day 16), 36, 48 (Day 17), 72 (Day 18), 96 (Day 19), 120 (Day 20), 144 (Day 21), 168 (Day 22), 192 (Day 23), 216 (Day 24), 240 (Day 25), 264 (Day 26) hours postdose or at ET.

[f]Blood samples for itraconazole and hydroxy-itraconazole PK will be collected predose and at 2.5 hours postdose on Days 13, 14, and 15.

[g]Collected predose.

Table 1.3-2 Schedule of Assessments - Part 2

Period	Screening		Treatment												Follow-up Phone Call 30 (+2) days after last dose of OPC-167832	Notes
Visit	Screening	Check-in	Period 1			Period 2										
Trial Day	−28 to −2	−1	1	2	3 to 7	8	9 and 10	11 to 13	14 to 22	23 and 24	25	26	27 to 31	32 End-of-Trial or ET		
ENTRANCE/HISTORY																
Informed Consent	X															Section 10.1.2
Demographics	X															Section 5.1
Inclusion/Exclusion Criteria	X	X														Section 5.2
Medical History	X															
Height	X															Section 8.5.2
Body Weight	X	X												X		Section 8.5.2
Body Mass Index	X	X														Section 8.5.2
Serology (HIV, HBsAg, anti-HCV)	X															Section 10.2
Urine alcohol and urine drug screen	X	X														Section 10.2
Urine pregnancy test (for FOCBP)	X	X												X		Section 10.3
FSH (for postmenopausal females)	X															Section 10.2
TRIAL RESIDENCY																
Check-in to trial site clinic		X														
Discharge from Clinic														X[a]		
SAFETY																
Adverse Events[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.6.1

Table 1.3-2 Schedule of Assessments - Part 2

Period	Screening		Treatment												Follow-up Phone Call 30 (+2) days after last dose of OPC-167832	Notes
Visit	Screening	Check-in	Period 1			Period 2										
Trial Day	−28 to −2	−1	1	2	3 to 7	8	9 and 10	11 to 13	14 to 22	23 and 24	25	26	27 to 31	32 End-of-Trial or ET		
Physical Examination[c]	X	X				X			X		X			X		Section 8.5.2
Vital Signs[d]	X	X	X	X		X	X		X		X	X		X		Section 8.5.3
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
12-Lead ECG[e]	X	X	X	X		X	X		X		X	X		X		Section 8.5.4
Laboratory Tests (hematology, serum chemistry, and urinalysis [with cell count])[f]	X	X				X		X	X		X			X		Section 8.5.1
C-SSRS[g]	X	X												X		Section 8.5.5
IMP ADMINISTRATION																
OPC-167832			X								X					Section 6.1
Carbamazepine[h]						X	X	X	X	X	X	X	X			Section 6.1
PHARMACOKINETICS																
Blood Samples for OPC-167832 PK[i]			X	X	X	X					X	X	X	X		Section 8.2.1
Blood Samples for Carbamazepine PK[j]										X	X					Section 8.2.1
OTHER PROCEDURES																
CCI [redacted]																

Table 1.3-2 Schedule of Assessments - Part 2

Period	Screening		Treatment												Follow-up Phone Call 30 (+2) days after last dose of OPC-167832	Notes
Visit	**Screening**	**Check-in**	**Period 1**			**Period 2**										
Trial Day	**−28 to −2**	**−1**	**1**	**2**	**3 to 7**	**8**	**9 and 10**	**11 to 13**	**14 to 22**	**23 and 24**	**25**	**26**	**27 to 31**	**32 End-of-Trial or ET**		
Medication Compliance Evaluation			X			X	X	X	X	X	X	X	X			Section 6.4

[a]An optional in-clinic observation after the completion of the treatment period is permitted, at the discretion of the Principal Investigator. During this period of optional observation, trial participants will be kept under direct clinical observation and may have unscheduled safety procedures performed as indicated and/or as determined by site medical staff.

[b]If an adverse event suspected to be related to administration of carbamazepine is recorded, the investigator should consider performing additional hematology tests to monitor for myelosuppression.

[c]Complete physical examinations will be performed at screening, predose on Days 8, 14, 25, and prior to discharge on Day 32 or at ET. A targeted physical examination will be completed at check-in and at any time per the investigator's discretion.

[d]Vital signs will be measured at screening, on Day −1, predose on Days 1, 2, 8, 9, 14, 25, 26 and prior to discharge on Day 32 or at ET.

[e]Twelve-lead ECGs will be performed at screening, on Day −1, predose on Days 1, 8, 14, 25, 3 hours after OPC-167832 administration on Days 1 and 25 and 24 hours after OPC-167832 administration on Days 1 and 25 (Days 2 and 26, respectively), 6 hours after morning administration of carbamazepine on Days 8 and 14, and 24 hours postdose after morning administration of carbamazepine on Days 8 and 14 (Days 9 and 15, respectively), and prior to discharge on Day 32 or at ET.

[f]Blood samples for clinical laboratory tests be collected on at screening, on Day −1, predose on Days 8, 11, 14, 25, and prior to discharge on Day 32 or at ET.

[g]Suicidality monitoring via C-SSRS will be performed at screening, on Day −1, prior to discharge on Day 32 or at ET, and at any other time point at the discretion of the investigator.

[h]Subjects will receive 100 mg carbamazepine in the mornings and evenings on Day 8 through Day 10, 200 mg carbamazepine in the mornings and evenings on Day 11 through Day 13, and 300 mg carbamazepine in the mornings and evenings on Day 14 through Day 31.

[i]Blood samples for OPC-167832 PK will be collected on predose Day 1 and at 1, 2, 3, 4, 8, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5) 120 (Day 6), 144 (Day 7), 168 (Day 8) hours postdose; and predose Day 25 and at 1, 2, 3, 4, 8, 12, 24 (Day 26), 36, 48 (Day 27), 72 (Day 28), 96 (Day 29), 120 (Day 30), 144 (Day 31), and 168 (Day 32) hours postdose or at ET.

[j]Blood samples for carbamazepine PK will be collected predose and at 6 hours postdose on Days 23, 24, and 25. Note: The PK collection on each of these days is relative to the morning dosing only, ie, predose PK collection prior to the morning dose followed by 6-hour postdose collection following the morning dose.

[k]Collected predose.

2 Introduction

OPC-167832 is an antimycobacterial small molecule currently being developed for the treatment of tuberculosis (TB; an infectious disease caused by *M tuberculosis*), with a novel mechanism of inhibition of decaprenylphosphoryl-β-D-ribose 2'-oxidase, an essential enzyme for cell wall biosynthesis. Potent antimycobacterial activity has been demonstrated in preclinical experimental models of chronic TB and early phase clinical trials in patients with drug-susceptible (DS) pulmonary TB.[1]

OPC-167832 has been evaluated in 3 clinical trials thus far. One completed phase 1 single-ascending dose Trial (323-201-00001) evaluated the dose range of 30 to 480 mg in healthy subjects and showed OPC-167832 is well tolerated without serious adverse events (SAE) or adverse events (AE) leading to discontinuation. Two studies are currently ongoing: a phase 1b/2a multiple-ascending dose trial (Trial 323-201-00003, 3-90 mg once daily [QD] for 14 days in Part I) in uncomplicated, smear-positive, DS pulmonary TB patients, in which preliminary exposure-response results showed that 30 mg and above is associated with maximum response in terms of colony-forming-unit (CFU) reduction. CCI [redacted]. CCI [redacted].

Please refer to the Investigator's Brochure (IB) for more detailed information on nonclinical data and clinical data for OPC-167832.

2.1 Trial Rationale

In vitro assessments indicate that OPC-167832 is metabolized primarily via cytochrome P450 (CYP) 3A enzyme isoforms with lesser involvement by CYP1A1 and CYP2C19.[2] Additionally, in vitro evaluation indicated that OPC-167832 was not a substrate for P-glycoprotein and breast cancer resistance protein transporters.[3,4]

There is a potential for exposure to different drug combinations and potential DDIs resulting from either the induction or inhibition of CYP drug-metabolizing enzymes. More specifically, since in vitro studies indicate that is a primary CYP isoform involved in the in vitro metabolism of OPC-167832, a thorough understanding of the potential DDI risk involving these pathways is essential for the development of this compound. This trial intends to assess the potential effects of CYP3A inhibitor (itraconazole) and CYP3A inducer (carbamazepine) on the metabolism of OPC-167832 in healthy adult subjects.

2.2 Background

2.2.1 Nonclinical Data

Please refer to the IB for a summary of nonclinical data for OPC-167832.

2.2.2 Clinical Data

Currently, one phase 1 human study (single-ascending dose Trial 323-201-00001) has been completed. Two studies are currently ongoing: a phase 1b/2a trial (Trial 323-201-00003) to assess the safety, tolerability, pharmacokinetics (PK), and efficacy of multiple doses of OPC-167832 in adult subjects with uncomplicated, smear-positive, DS pulmonary TB and a phase 1 trial (Trial CCI) CCI Additionally, a phase 2b/c study evaluating the safety and efficacy of a 4-month regimen of OPC-167832 in combination with delamanid and bedaquiline in participants with DS pulmonary TB is planned (Trial 323-201-00006).

In healthy subjects, a single-ascending dose trial (Trial 323-201-00001) has been completed and a multiple-ascending dose and early bactericidal activity trial is ongoing in subjects with DS-TB (Trial 323-201-00003). Preliminary exposure-response analysis showed that 30 mg or above is associated with maximum CFU reduction activity and the tested dose range of 10, 30, and 90 mg was associated with exposure (and the area under the concentration-time curve [AUC]) above the mean CCI of maximal effective concentration value; OPC-167832 has similar terminal half-life at steady-state as after a single-dose.

In general, a less-than dose dependent increase in plasma exposure was observed for OPC-167832 in healthy subjects and DS-TB patients. The median terminal half-life (C CI of OPC-167832 supported a daily dosing regimen in DS-TB patients. There was a positive food effect for OPC-167832, which the maximum (peak) plasma concentration of the drug (C_{max}) of approximately CCI increase and the area under the concentration-time curve (AUC) of approximately CCI increase following standard meal as compared to fasted state was observed, and the difference of high-fat versus standard meal was small.

Please refer to the IB for more detailed information on nonclinical data and clinical data for OPC-167832.[1]

2.3 Known and Potential Risks and Benefits

Subjects will receive no health benefit from participation in this trial.

Single oral doses up to 480 mg OPC-167832 were well tolerated during Trial 323-201-00001; there were no serious or severe AEs and no subjects were discontinued from the trial due to a treatment-emergent AE. One subject did decide to withdraw consent after occurrence of the nonserious and mild AEs of arthralgia, pain in extremity, and ecchymosis.[1] There was a slight negative correlation observed between changes in QT interval corrected for heart rate using Fridericia's formula (QTcF) from baseline and placebo, and OPC-167832 plasma concentrations. There is currently 1 ongoing trial (Trial 323-201-00003) that is evaluating the safety of OPC-167832 in adult subjects with uncomplicated DS pulmonary TB. There was 1 SAE of haemoptysis (3 mg group in Stage 1), which led to discontinuation of investigational medicinal product (IMP). This SAE was not considered to be causally related to the IMP but as a complication of the underlying pulmonary TB. There was 1 SAE of anal abscess (30 mg OPC-167832 and 400 mg bedaquiline group in Stage 2), which led to discontinuation of IMP and was considered unrelated to the IMP.[1]

In 1-, 4-, and 26-week toxicity studies in rats, no drug-related deaths occurred in either males or females at any dose tested. Suppressed body weight gain and/or decreased food consumption were observed and increases in total cholesterol and phospholipids and decreases in creatinine were observed at 1 week. These changes showed reversibility or a tendency for reversibility.

In 1-, 4-, 13- and 39-week toxicity studies in dogs, no treatment related deaths occurred in either males or females at any dose tested. Increases in creatinine kinase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, and potassium were observed in the 4-week toxicity study at the highest dose (2000 mg/kg/day). Increases in total cholesterol and phospholipids were also observed in the 4- and 13-week toxicity studies at doses of 100 mg/kg/day and higher. In the 4-week toxicity study, slight prolongation of QT interval and QTc was observed at Week 4 in both sexes at 2000 mg/kg/day. However, no prolongation of QT interval and QTc was noted in the 13-week toxicity study in either sex at up to 100 mg/kg.

In 4- and 13-week repeated dose oral toxicity studies in dogs, decreased body weight or suppressed body weight gain, or both, and decreased food consumption were observed. In histopathological examination, degeneration of muscle was fiber observed in both sexes at doses of 10 mg/kg and greater. These changes showed reversibility or a tendency for reversibility.[1]

Safety information on the CYP inhibitors and inducers that will be used in this trial can be found in their United States Prescribing Information (USPI).

The trial site will receive updated versions of the IB, when available, and the trial site should always refer to the most current version as needed.

3 Objectives and Endpoints

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To assess the potential for CYP-mediated drug-drug interactions with OPC-167832: • Inhibition of OPC-167832 metabolism via CYP3A by itraconazole • Induction of OPC-167832 metabolism via CYP3A by carbamazepine	Primary: OPC-167832 PK: C_{max}, AUC_t, and AUC_∞
Secondary: To assess the safety and tolerability of OPC 167832 administered alone or in combination with itraconazole or carbamazepine	Secondary: Safety: AEs, clinical laboratory tests, vital signs, physical examinations, 12-lead ECGs, and C-SSRS (Part 2 only)

AE = adverse event; AUC_∞ = area under the concentration-time curve from time zero to infinity; AUC_t = area under the concentration-time curve calculated to the last observable concentration at time t; C_{max} = maximum (peak) plasma concentration of the drug; C-SSRS = Columbia-Suicide Severity Rating Scale; CYP = cytochrome P450; ECG = electrocardiogram; PK = pharmacokinetics.

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This is a single-center, 2-part, open-label DDI trial in healthy adult subjects. Part 1 and Part 2 will have fixed sequence designs with 12 subjects in each part for a total of 24 subjects enrolled.

- Part 1: OPC-167832 + itraconazole (strong CYP3A inhibitor)
- Part 2: OPC-167832 + carbamazepine (strong CYP3A inducer)

Following a screening period of up to 28 days, eligible subjects will enter the clinic on the day prior to the first treatment day (Day −1).

For Part 1, the impact of CYP3A inhibition on the PK of OPC-167832 will be assessed. Subjects will receive a single, 30-mg, oral dose of OPC-167832 CCI [redacted] in the fasted state on Day 1 with blood collections for PK assessment of OPC-167832 from Day 1 through Day 8. On Day 8, subjects will receive 200-mg doses of itraconazole in the morning and evening (200 mg twice daily [BID]) followed by 200 mg of itraconazole administered QD on Day 9 through Day 14 to approach steady-state conditions for itraconazole. On Day 15, a single, 30-mg, oral dose of OPC-167832 CCI [redacted] will

be administered concurrently with a 200-mg dose of itraconazole in the fasted state with blood collections for PK assessment of OPC-167832 from Day 15 through Day 26. Once daily 200-mg doses of itraconazole will continue to be administered on Day 16 through Day 25. Subjects will be discharged from the clinic after the PK sample on Day 26 or early termination (ET).

For Part 2, the impact of CYP3A induction on the PK of OPC-167832 will be assessed. Subjects will receive a single, 30-mg, oral dose of OPC-167832 CCI on Day 1 in the fasted state with blood collections for PK assessment of OPC-167832 from Day 1 through Day 8. On Day 8 through Day 10, subjects will receive 100 mg BID carbamazepine followed by 200 mg BID carbamazepine administration on Day 11 through Day 13 and 300 mg BID carbamazepine administration on Day 14 through Day 31. On Day 25, a 30-mg oral dose of OPC-167832 CCI will be administered concurrently with the morning 300 mg dose of carbamazepine in the fasted state with blood collections for PK assessment of OPC-167832 from Day 25 through Day 32. Subjects will be discharged from the clinic after the PK sample on Day 32 or ET.

All subjects will be contacted by phone 30 days after the last dose of OPC-167832 to assess any new or ongoing AEs and to record concomitant medications.

Blood samples will be collected during the trial for analysis of OPC-167832 plasma concentrations, as well as itraconazole and hydroxy-itraconazole or carbamazepine plasma concentrations in select blood samples. CCI

Schedule of assessments (SoA) are provided in Table 1.3-1 (Part 1) and Table 1.3-2 (Part 2).

4.2 Scientific Rationale for Trial Design

This trial will be open-label as the primary endpoints are objective rather than subjective. The crossover design in both Part 1 and Part 2 allows subjects to serve as their own control, with the reduced intra-subject variability.

Part 1 of the trial will assess the potential effect of the CYP3A inhibitor itraconazole on the metabolism of OPC-167832 in healthy adult subjects.

Part 2 of the trial will assess the potential effect of the CYP3A inducer carbamazepine on the metabolism of OPC-167832 in healthy adult subjects.

4.3 Dosing Rationale

The trial is designed with 2 parts to separately evaluate the potential for DDIs between OPC-167832 and either itraconazole (inhibition of CYP3A, Part 1) or carbamazepine (induction of CYP3A, Part 2). The OPC-167832 dose of 30 mg will be administered [redacted] under fasted conditions. OPC-167832 [redacted] 30 mg was considered a clinically-relevant dose according to the preliminary results from the multiple-ascending dose/early bactericidal activity trial (Trial 323-201-00003). The potential higher plasma exposure of approximately 5- to 6-fold (C_{max} and AUC) with itraconazole would be within the safety margin of highest tested clinical dose of 480 mg of OPC-167832 (Trial 323-201-00001).

Itraconazole (200 mg given QD as 10-mg/mL solution) is the recommended regimen for strong CYP3A inhibition.[5] A loading dose of 200 mg BID every 12 hours on the first day of itraconazole administration (Day 8) followed by QD administration of 200 mg allows for more rapid attainment of itraconazole steady-state conditions. Once daily dosing of itraconazole will be continued through Day 25.

Carbamazepine was selected for administration in Part 2 because it is cited as a CYP3A inducer in the Food and Drug Administration table "Examples of clinical inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)".[6] Literature studies conducted in healthy subjects used carbamazepine doses ranging from 200 to 1200 mg/day, with the majority of studies conducted with 400 mg/day or 600 mg/day.[7] The physiologically based PK simulation showed that 600 mg/day approached the plateau of induction. Given titration may be needed to improve the tolerability and reduce drop-out rate, carbamazepine was usually initiated from 100 mg BID and titrate to 300 mg BID over 3 to 7 days and then maintain at 300 mg BID for 14 days to reach the maximum effect. Therefore, 100 mg BID carbamazepine will be administered for 3 days, followed by dosing of 200 mg BID for 3 days, then 300 mg BID for 10 days. Twice daily dosing of 300 mg carbamazepine will be continued through Day 31.

4.4 Start and End-of-Trial Definitions

The trial start is defined as the first visit of the first subject, which is the date the first subject signs their informed consent/assent form.

The end-of-trial date is defined as the last date of contact, or the date of final contact attempt as recorded on the post-treatment follow-up electronic case report form (eCRF) page for the last subject completing or withdrawing from the trial.

4.5 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually takes all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects in Part 1 who complete the last scheduled PK assessment on Day 26 and subjects in Part 2 who complete the last scheduled PK assessment on Day 32 will be defined as trial completers.

5 Trial Population

Twenty-four subjects in total will be enrolled in the trial, with 12 subjects enrolled in each part, such that approximately 10 healthy male or female subjects, 18 to 55 years of age, inclusive, complete each part of the trial. Discontinued subjects may be replaced at the discretion of the sponsor.

5.1 Subject Selection and Numbering

All subjects will be given a unique subject identifier (ID; site number [3 digits] + subject number ['S' + 5 digits] upon providing consent [or assent, if applicable]). The site number will be designated by the sponsor. For each site, the subject number will be given sequentially from S00001.

Demographic information (collection date, date of birth, sex at birth, gender identification, childbearing potential, race, ethnicity) and medical history will be recorded in the eCRF at the screening visit.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the medical monitor.

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria when assessed:

1) Male or female subjects between 18 and 55 years of age, inclusive.
2) BMI between 19.0 to 32.0 kg/m^2, inclusive.
3) In good health at screening as determined by:
   a) Medical history
   b) Physical examination
   c) Twelve-lead electrocardiogram (ECG)
   d) Serum/urine chemistry, hematology, and serology tests.

4) Ability to provide written, informed consent prior to initiation of any trial-related procedures, and ability, in the opinion of the principal investigator, to comply with all the requirements of the trial.

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria when assessed:

1) Clinically significant abnormality in past medical history, or at the screening physical examination, that in the investigator's or sponsor's opinion may place the subject at risk or interfere with outcome variables including absorption, distribution, metabolism, and excretion of drug. This includes, but is not limited to, any of the following diseases/disorders (concurrent or history of): cardiac, hepatic, renal, neurologic, endocrine, gastrointestinal, respiratory, hematologic, immunologic disease, and previous history of cholecystectomy.
2) History of drug and/or alcohol abuse (as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for moderate to severe alcohol/substance use disorder) within 2 years prior to the screening visit.
3) History of or current hepatitis or acquired immunodeficiency syndrome or carriers of hepatitis B surface antigen, hepatitis C antibodies, and/or human immunodeficiency virus antibodies.
4) History of any clinically significant drug allergy or known or suspected hypersensitivity, to any component of the IMP including structurally related drugs (eg, tricyclic antidepressants), hereditary fructose intolerance (Part 1 only), or any of the excipients.
5) A positive urine alcohol test and/or urine drug screen for substances of abuse at the screening visit or upon check-in to the trial site.
6) Subjects having taken an investigational drug within 30 days prior to the screening visit.
7) Any history of clinically significant hemorrhagic tendencies.
8) A history of difficulty in donating blood.
9) The donation of blood or plasma within 30 days prior to the first dose of IMP.
10) Consumption of alcohol, food, or beverages containing methylxanthines, pomelo, star fruit, grapefruit, grapefruit juice, Seville oranges, or Seville orange juice within 7 days prior to the first dose of IMP.
11) Use of prescription, over-the-counter, herbal medications, or vitamin supplements within 14 days prior to the first dose of IMP and antibiotics or dietary supplements (eg, creatine) within 30 days prior to the first dose of IMP. The sponsor may allow exceptions only if the medication's administration is deemed unlikely to affect the PK result.
12) Having received a vaccine within 14 days prior to dosing.

13) Exposure to any substances known to stimulate hepatic microsomal enzymes within 30 days prior to the screening visit (eg, occupational exposure to pesticides, organic solvents).
14) Use of tobacco products, nicotine replacement therapies, e-cigarettes, or daily exposure to second-hand smoke within 2 months prior to the screening visit, urine cotinine concentrations > 200 ng/mL, or serum cotinine concentrations > 20 ng/mL, at the screening visit or at check-in.
15) Subjects who have supine blood pressure, after resting for at least 5 minutes, > 140 mmHg or < 100 mmHg (systolic blood pressure) or > 90 mmHg or < 50 mmHg (diastolic blood pressure) at the screening visit or check-in. If the blood pressure is outside of the specified ranges but is not deemed clinically significant, a total of 3 readings will be taken 10 minutes apart. The subject will be included in the trial if 2 out of 3 readings are within the specified ranges.
16) Abnormal ECG findings at screening or check-in, as follows:
    a) A QTcF > 450 msec (males) or QTcF > 470 msec (females).
    b) QRS interval > 120 msec.
    c) PR interval > 200 msec.
17) Subjects who have a supine heart rate, after resting for at least 5 minutes, outside the range of 50 to 90 beats per minute at the screening visit or at check-in. If the heart rate is outside of the specified range but is not deemed clinically significant, a total of 3 readings will be taken 10 minutes apart. The subject will be included in the trial if 2 out of 3 readings are within the specified range.
18) Any subject who, in the opinion of the investigator, should not participate in the trial.
19) Female subjects who are breast-feeding or who have a positive pregnancy test result prior to receiving IMP.
20) Sexually active males or females of childbearing potential (FOCBP), or their partners, who do not agree to practice 2 different approved methods of birth control or remain fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] or withdrawal are not acceptable methods of contraception) during the trial and for 90 days after the last dose of IMP. If employing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, nonhormonal intrauterine device, birth control pill, birth control implant, birth control depot injection, birth control patch, condom with spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide. For FOCBP enrolled in Part 2 of the trial, if employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, nonhormonal intrauterine device, condom with spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide due to potential of carbamazepine to reduce the efficacy of hormonal contraceptive methods.
21) Male subjects who do not agree to refrain from donating sperm from trial screening through 90 days after the last dose of IMP.

22) Female subjects who do not agree to refrain from donating eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction from trial screening through 6 months after the last dose of IMP.
23) Subjects without a permanent physical residence.
24) History of suicide ideation or severe depression that, in the opinion of the investigator, would exclude the subject from participating in this trial (applicable to Part 2 only).
25) Platelets, red blood cell count, neutrophils, white blood cell count, or hemoglobin below the lower limit of normal. A single repeat is allowed. (Applicable to Part 2 only).
26) History of hepatic porphyria or previous bone marrow depression (eg, prior viral or drug-related bone marrow depression) (applicable to Part 2 only).
27) Subjects of Asian descent or ancestry (applicable to Part 2 only).

A definition of childbearing potential can be found in Section 10.3.

Subjects must agree to restrictions to medications and lifestyle described in Section 6.5 and Section 5.3, respectively.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Consumption of alcohol, food, or beverages containing methylxanthines, pomelo, star fruit, grapefruit, grapefruit juice, Seville oranges, or Seville orange juice within 7 days prior to the first dose of IMP and during the treatment period of the trial.

5.3.2 Caffeine, Alcohol, and Tobacco

The use of tobacco products, nicotine replacement therapies, e-cigarettes, or daily exposure to second-hand smoke within 2 months prior to the screening visit is prohibited. Urine cotinine concentrations > 200 ng/mL or serum cotinine concentrations > 20 ng/mL at screening or at check-in is prohibited. The consumption of alcohol is prohibited within 7 days prior to dosing and during the treatment period of the trial.

5.3.3 Physical Activity

Subjects should avoid strenuous activity within 24 hours prior to check-in until end-of-trial. On serial PK sampling days (Days 1 and 15 in Part 1and Days 1 and 25 in Part 2), subjects will remain either in a seated or semi-recumbent position for the first 4 hours following dosing except during brief periods where protocol-related procedures need to be performed. Restroom visits must be supervised during the 4 hours postdose and should be brief (< 10 minutes). In addition, during the 4-hour period after oral dosing, the subject's toilet use must be supervised to prevent self-induced emesis resulting in loss of

the oral dose. Following the 4-hour postdose period, the subjects will be allowed to ambulate but should not exercise strenuously.

5.4 Screen Failures

A screen failure is a subject from whom informed consent/assent is obtained and is documented in writing (ie, subject signs an informed consent form [ICF]), but who is not assigned trial intervention(s). All AEs must be reported after subject informed consent/assent has been obtained, including screen failures due to AEs, irrespective of trial intervention administration. Subjects with a positive drug or alcohol screen are not eligible to be rescreened for participation in the trial; however, subjects excluded for other reasons may be rescreened at any time at the discretion of the medical monitor if the exclusion characteristic has changed or resolved. In the event that the subject is rescreened for trial participation, and the rescreening is not completed within the protocol-specified screening period, a new ICF must be signed and screening procedures repeated. Rescreened subjects should also be assigned a new subject number for every screening/rescreening event.

If the subject meets the definition of a screen failure in this trial, the following information will be recorded in the eCRF:

- Date of ICF signature
- Visit date (screening visit)
- Demographics (collection date, birth date, sex, race, ethnicity)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure
- Any AEs

6 Trial Intervention(s) and Concomitant Therapy

6.1 Trial Intervention(s) Administered

Trial interventions are all pre-specified, investigational and noninvestigational medicinal products intended to be administered to the subjects during the conduct of the trial.

OPC-167832, itraconazole, and carbamazepine will be administered orally to subjects as per the dosing schedule in Table 6.1-1. OPC-167832 CCI [redacted] will be provided as 30-mg tablets, itraconazole will be administered as a 10-mg/mL oral solution, carbamazepine will be administered as the least number of tablets based on commercially available extended-release tablets (ie, 100-mg tablet, 200-mg tablet). Lower dose strengths of carbamazepine can be combined, ie, a 100-mg tablet and a 200-mg tablet

should be combined to dose at 300 mg. All doses will be administered with approximately 240 mL of room temperature, still water. When itraconazole is administered, some of the 240 mL of water should be used to rinse the dosing container. All doses of OPC-167832 (administered on Days 1 and 15 in Part 1 and Days 1 and 25 in Part 2) will be administered following an overnight fast of at least 10 hours.

For Part 1, OPC-167832 and itraconazole will be administered in the morning at the same time each day. The BID dose of itraconazole on Day 8 will be administered every 12 hours (q12h). On days of serial PK sampling days (Days 1 and 15), subjects will be required to continue to fast from food for at least 4 hours following dosing of OPC-167832 and water will be restricted for 1 hour before to 2 hours after dosing of OPC-167832. Water is permitted ad libitum on all other days.

For Part 2, OPC-167832 and carbamazepine will be administered in the mornings at the same time each day and BID doses of carbamazepine will be administered q12h and at same time each evening. On days of serial PK sampling days (Days 1 and 25), subjects will be required to continue to fast from food for at least 4 hours following dosing of OPC-167832 and water will be restricted for 1 hour before to 2 hours after dosing of OPC-167832. Water is permitted ad libitum on all other days.

For information regarding the dosage regimen and treatment period(s), including any follow-up period(s) for each treatment group/part of the trial, see Section 4.1.

Table 6.1-1 Dosing Schedule

Study Day	Time	Dose
PART 1		
1	morning	30 mg OPC-167832
8	morning	200 mg itraconazole
	evening	200 mg itraconazole
9 through 14	morning	Once-daily 200 mg itraconazole
15	morning	30 mg OPC-167832 and 200 mg itraconazole
16 through 25	morning	Once-daily 200 mg itraconazole
PART 2		
1	morning	30 mg OPC-167832
8 through 10	morning	100 mg carbamazepine extended release
	evening	100 mg carbamazepine extended release
11 through 13	morning	200 mg carbamazepine extended release
	evening	200 mg carbamazepine extended release
14 through 24	morning	300 mg carbamazepine extended release[a]
	evening	300 mg carbamazepine extended release[a]
25	morning	30 mg OPC-167832 and 300 mg carbamazepine extended release[a]
	evening	300 mg carbamazepine extended release[a]

Table 6.1-1 Dosing Schedule		
Study Day	**Time**	**Dose**
26 through 31	morning	300 mg carbamazepine extended release[a]
	evening	300 mg carbamazepine extended release[a]

[a]Lower dose strengths of carbamazepine can be combined, ie, a 100-mg tablet and a 200-mg tablet should be combined to dose at 300 mg.

6.2 Management of Trial Intervention(s)

For full details on management of trial intervention(s), please refer to the trial-specific operations manual.

6.2.1 Packaging and Labeling

OPC-167832 will be provided by the sponsor or designated agent to the investigators and the persons designated by the investigator(s) or institution(s). OPC-167832 will be supplied in bottles. OPC-167832 may not be repackaged by the trial site. Each bottle used in the dosing period will be labeled to clearly disclose the compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements and other information required by local regulatory authorities. The clinical site will be responsible for purchasing itraconazole and carbamazepine required for this trial.

6.2.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees.

The IMP will be stored according to the conditions indicated on the IMP label.

The trial site staff will maintain a temperature log in the IMP storage area to record the temperature.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational or active control) received, dispensed, administered, and destroyed. Neither the investigator nor any designees may provide IMP to any subject not participating in this trial.

6.2.4 Returns and Destruction

The IMP may only be destroyed by the trial site if approved by the sponsor and if the IMP destruction meets all local regulations. The IMP will be destroyed by the clinical trial site following completion and verification of accountability of the IMP by the

assigned trial monitor. The trial site may utilize qualified third-party vendors for IMP destruction. A certificate of destruction should be filed within the IMP accountability.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, consumer, clinical trial subject, medical representative, regulatory agency, partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device or medicinal product or a falsified, tampered, or diverted product after it is released for distribution.

Examples include, but are not limited to, communications involving:

- Failure/malfunction of a medicinal product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Bottle defects (eg, under-fill, over-fill, no safety seal)
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record each PQC identified through any means from the receipt of the trial intervention(s) from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Send PQC reporting information (listed in Section 6.2.5.2) to the Otsuka Pharmaceutical Development & Commercialization, Inc. IMP PQC mailbox email: CCI [redacted]

Identification of a PQC by the subject should be reported to the site investigator, who should then follow the reporting mechanism above.

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)

- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return
- Was any subject at risk due to the identified issue?

6.2.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide return instructions, when applicable.

It must be documented in the site accountability record that the complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

6.2.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

6.3 Measures to Minimize/Avoid Bias

This is an open-label trial; blinding and randomization procedures are not applicable.

6.4 Subject Compliance

The time and dose of IMP administration during the trial will be recorded on the eCRF. Information regarding any inappropriately administered doses will also be documented on the eCRF. All doses of IMP will be administered while the subjects are in the clinic; compliance will be ensured by a mouth check during the oral dosing administration of IMP.

6.5 Prior/Concomitant Medications or Therapies

The investigator will record all medications and therapies taken or medical procedures undergone by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) in the eCRF. The investigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the eCRF.

For concomitant medications, the following will be recorded in the eCRF: medication, indication, dose, frequency, route, start date and end date. For concomitant therapy, the following will be recorded in the eCRF: therapy, indication, start date and end date.

6.5.1 Prohibited Medications or Therapies

The use of prescription, over-the-counter, herbal medications, or vitamin supplements within 14 days prior to the first dose and during the treatment period of the trial are prohibited. Antibiotics or dietary supplements (eg, creatine) within 30 days prior to the first dose and during the treatment period of the trial are prohibited. Medications other than the protocol-specific trial interventions and the contraception specified in Appendix 10.3 are not to be taken during the trial; however, the sponsor may allow exceptions only if the medication is unlikely to affect the PK result.

6.5.2 Restricted Medications or Therapies

Not applicable.

6.5.3 Rescue Medications

Not applicable.

6.6 Intervention After the End of the Trial

Not applicable.

7 Discontinuation of Trial/Treatment and Subject Discontinuation/Withdrawal

7.1 Entire Trial or Treatment

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, institutional review boards (IRBs), and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site Discontinuation

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and Good Clinical Practice. The investigator will notify the sponsor promptly if the investigator or the IRB at the site discontinues participation in the trial.

7.3 Discontinuation of Trial Intervention

Under certain circumstances, it may be necessary for a subject to permanently discontinue trial intervention. If trial intervention is permanently discontinued, the subject should, if at all possible, remain in the trial to complete all ET and follow-up assessments with ET assessments conducted as soon as possible after the subject is withdrawn. See

the SoA for data to be collected at the time of discontinuation of trial intervention and follow-up and for any further evaluations that need to be completed. If a subject discontinues trial intervention due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized.

For each subject who discontinues trial intervention, the main reason for discontinuation will be recorded in the eCRF (refer to Section 7.4.1 Documenting Reasons for Subject Discontinuation/Withdrawal).

7.4 Subject Discontinuation/Withdrawal from the Trial

- A subject may withdraw from the trial at any time at the subject's own request for any reason (or without providing any reason).
- A subject may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the trial, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.
- If a subject withdraws consent from the trial, the subject will be permanently discontinued from all trial interventions and the trial.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before the withdrawal of consent.
- If a subject withdraws from the trial, the subject may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method, as agreed by subject and trial site staff).
- Contact of the subject by trial site staff, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue trial intervention administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3). Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

7.4.1 Documenting Reasons for Subject Discontinuation/Withdrawal

A subject may discontinue trial intervention(s) or withdraw from the trial for the reasons listed below:

- Adverse event
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
  - Serious adverse event
  - Other potentially IMP-related safety concerns or AEs
- Death
- Lost to follow-up
- Noncompliance with study IMP
- Physician decision
- Pregnancy
- Protocol deviation
- Protocol-specific withdrawal criterion met
- Site terminated by sponsor
- Withdrawal by subject

7.5 Lost to Follow-up

Subjects who do not complete the last scheduled PK assessment on Day 26 for Part 1 and Day 32 for Part 2 during the trial intervention period, who do not have a known reason for discontinuation (eg, withdrew consent/assent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up." Survival status can be determined from a variety of sources, either by obtaining acceptable documentation of death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation of

life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

If the subject was classified as "lost to follow-up," the following information will be recorded in the eCRF: "Date of final contact attempt" and "Contact method."

8 Trial Procedures

Schedules of assessments are provided in Table 1.3-1 (Part 1) and Table 1.3-2 (Part 2).

8.1 Efficacy Assessments

Not applicable.

8.2 Pharmacokinetic Assessments

8.2.1 Pharmacokinetic Blood Samples

Pharmacokinetic samples will be collected at the time points described in the SoA (Table 1.3-1 [Part 1] and Table 1.3-2 [Part 2]).

Blood samples (4 mL) for OPC-167832 PK analysis will be collected (an indwelling catheter is permitted) in vacutainers containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) and processed into plasma to determine the concentrations of OPC-167832. These samples should be collected within ± 3 minutes of the nominal time. Predose samples should be collected within 60 minutes before administration of OPC-167832.

Blood samples (2 mL) for itraconazole, hydroxy-itraconazole, and carbamazepine PK analysis will be collected in vacutainers (anticoagulant will be provided in the operations/laboratory manual) and processed into plasma to determine the concentrations of itraconazole, hydroxy-itraconazole, carbamazepine, and/or other metabolites, if applicable. These samples should be collected within ± 3 minutes of the nominal time. Predose samples should be collected within 10 minutes before administration of itraconazole or the morning doses of carbamazepine.

After processing into plasma, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70°C or −20°C, unless otherwise instructed in the trial-specific operations/laboratory manual.

When vital signs or ECGs are scheduled at the same nominal time as PK sample collections, vital signs should be measured and ECGs should be performed before PK samples are collected. The actual date and time of the PK sample collection will be recorded in the eCRF.

Blood samples will be analyzed to determine plasma concentrations of OPC-167382, itraconazole, hydroxy-itraconazole, and carbamazepine, as applicable. Metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, PK samples may be used for the investigation of a bioanalytical method, if needed.

All PK samples will be shipped to the bioanalytical laboratory. Additional information will be provided in the trial-specific operations/laboratory manual.

8.3 Biomarker Assessments

8.3.1 Pharmacodynamic Laboratory Tests

Not applicable.

8.3.2 Exploratory Biomarker Assessments

Not applicable.

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8.5 Safety Assessments

Safety assessments in this trial include AEs, clinical laboratory assessments, vital signs, 12-lead ECGs, physical examinations, and the Columbia-Suicide Severity Rating Scale ([C-SSRS] Part 2 only).

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.6.

8.5.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the SoA (Table 1.3-1 [Part 1] and Table 1.3-2 [Part 2]) to perform the clinical laboratory assessments described in Section 10.2. The total volume of blood to be collected during the trial will be documented in the electronic ICF. Vital signs should be measured and ECGs should be performed before any blood samples are collected. Refer to Section 8.6.6 for the evaluation and documentation of potential serious hepatotoxicity events. The Division of AIDS (DAIDS) Adverse Event Grading Tables will be used for identifying laboratory values of potential clinical relevance.[8] Any postscreening abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF. Refer to Section 8.6.2 for details on recording and reporting AEs.

8.5.2 Physical Examination

Physical examinations will be performed at the time points described in the SoA (Table 1.3-1 [Part 1] and Table 1.3-2 [Part 2]). The complete physical examination will include height (screening only), weight, and calculation of BMI (screening and check-in only) as well as assessment of the head, neck, eyes, ears, nose, and throat; thorax; abdomen; skin and mucosae; neurological; and extremities. A targeted physical examination, which is a review that focuses on subject-driven issues based on investigator judgment (eg, the investigator enquires if the subject has any complaints, pains, or disturbances and this would lead to further evaluation of the problematic area), will be completed at check-in, on Day 1 for both study Part 1 and Part 2 and can also be completed at any time per the investigator's discretion. Any postscreening abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF. Refer to Section 8.6.2 for details on recording and reporting AEs.

Whenever possible, the same individual should perform all physical examinations for any individual subject throughout the course of the trial. Individuals performing the physical examination must be permitted to do so by local regulations, must be listed on the FDA

Form 1572 as principal investigator or subinvestigator, and must be listed on the trial site delegation of authority form as performing this function.

8.5.3 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be collected at the time points described in the SoA (Table 1.3-1 [Part 1] and Table 1.3-2 [Part 2]). Vital signs will be obtained prior to ECGs and PK blood draws and at the nominal time points, where applicable. Blood pressure and heart rate will be obtained after the subject has been at rest in the supine position for at least 3 minutes. Temperature and respiratory rate will be taken with the subject in the supine position. Subjects should be monitored for potentially clinically significant vital signs values. Any postscreening abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF. Refer to Section 8.6.2 for details on recording and reporting AEs.

Refer to the trial-specific operations manual for the criteria for identifying vital sign measurements outside of age-specific normal reference ranges.

8.5.4 Electrocardiogram

Twelve-lead ECGs will be performed at the time points described in SoA (Table 1.3-1 [Part 1] and Table 1.3-2 [Part 2]).

Twelve-lead ECGs will be performed with the subject in the supine position for at least 10 minutes prior to each measurement. Single ECGs will be performed at all time points except for check-in when they should be performed in triplicate, with the average of the 3 values will be the baseline value. Electrocardiograms will be performed after vital signs and prior to PK blood draws and at the nominal time points, where applicable.

Subjects' ECGs should be monitored and assessed for potential clinical significance. Any postscreening abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE eCRF. Refer to Section 8.6.2 for details on recording and reporting AEs.

The ECG data will be captured manually in the eCRF. The principal investigator or licensed physician delegated to do so must review, sign, and date each ECG reading. The reviewer must be listed on the FDA Form 1572 and the site delegation of responsibility form.

8.5.5 Suicidality Monitoring

Suicidality monitoring will occur only in subjects enrolled in Part 2 and at the time points described in the SoA (Table 1.3-2).

Carbamazepine is known to increase the risk for suicidal ideation, thoughts, or behaviors in the psychiatric patient population. Therefore, for central-nervous-system safety, the C-SRRS test will be conducted at screening and check-in to exclude subjects with suicidal ideation and prior to discharge to ensure subjects' safety with regard to suicidal ideation behavior. If, during study conduct, a subject develops depressive symptoms, the C-SSRS test may be administered at the investigator's discretion.

The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior has occurred. The interview and rating for the C-SSRS must be completed by a licensed clinician or designee who has completed the required rater training to complete this assessment and who has been approved by the sponsor to administer this assessment. Documentation of training should be maintained in the trial site's files.

The "Baseline/Screening" version of the C-SSRS will be completed at screening and the "Since Last Visit" version will be completed at all other specified visits (including ET, if applicable). The "Baseline/Screening" version be used to assess Suicidal Ideation and Suicidal Behavior in both the subjects' lifetime and within the past 12 months prior to screening. There are a maximum of 19 items to be completed: 7 required, 10 potential additional items if there is a positive response to a required item, and 2 items for suicide/suicide behavior present during the interview. The C-SSRS uses dichotomous scales (ie, yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors.

8.6 Adverse Events

8.6.1 Definitions

Trial interventions are all pre-specified, investigational and noninvestigational medicinal products, intended to be administered to the subjects during the conduct of the trial.

Adverse Event: An AE is defined as any untoward medical occurrence in a clinical trial subject administered a trial intervention and which does not necessarily have a causal relationship with this intervention. Adverse events would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to a trial intervention related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the trial intervention caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the trial intervention and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of IMP treatment. In more detail, TEAEs are all AEs which started after the start of IMP; or if the event was continuous from baseline and worsens either in intensity or frequency, becomes serious, is assessed as IMP-related or results in death.

A Serious Adverse Event (SAE) includes any event that results in any of the following outcomes:

- Death.
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
- Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE and should be recorded as medical history.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Adverse Events of Special Interest (AESIs): A noteworthy event for the particular IMP or class of products that a sponsor may wish to monitor carefully. All AESIs are to be reported as immediately reportable events (IREs). No AESIs have been identified for the IMP to be administered during this trial.

Immediately Reportable Event:

- Any SAE.
- Potential serious hepatotoxicity (see Section 8.6.6).
- Any AE related to occupational exposure (eg, an investigator getting a skin rash after exposure to a medication). Non-subject AEs would not be recorded on the eCRF form but must be recorded on an IRE form to the sponsor.
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, pregnancy of a trial subject will mandate trial intervention discontinuation and pregnancy of either a subject or a subject's partner must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. This includes pregnancy of the subject or the partner of the subject. Pregnancy will only be documented on the AE eCRF if the pregnancy occurs in a female subject and there is an abnormality or complication (see Section 10.3).

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of laboratory tests for each individual subject as they become available. This review will be documented by the investigator's dated signature on the laboratory report. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in the eCRF. The severity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

8.6.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be

recorded on the source documents and eCRF provided by the sponsor. Adverse event collection will begin after a subject, or parent/legal guardian, signs the ICF, and will continue until the 30-day follow-up phone call. All AEs must be reported after subject informed consent/assent has been obtained, including screening failures due to AEs, irrespective of trial intervention administration.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

Medical or surgical procedures (eg, endoscopy, appendectomy) should not be reported as AEs; however, the condition that led to the procedure may be reported as an AE.

If a reported AE undergoes a change or worsening in severity, seriousness, or toxicity, it should be reported as a new AE in the eCRF.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 8.6.3. Special attention should be paid to recording hospitalization and concomitant medications.

The AE, start date, end date (if possible, start date and time, end date and time), seriousness, severity, relationship to IMP (causality), action taken with IMP, and outcome will be recorded on the source documents and in the eCRF.

Note: Start time should be recorded in the event an AE such as vomiting occurs. When capturing start/end time, at a minimum, the hour should be captured in the event it is difficult to specify in hours and minutes.

Regarding SAE, relationship to, and action taken with trial intervention(s) other than IMP will also be evaluated per each intervention. These evaluations will be recorded in the source documents and in the eCRF and will be reported using the IRE form (see Section 8.6.3).

8.6.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after he/she or site personnel become aware of any IRE (SAE, AE related to occupational exposure, potential serious hepatotoxicity, or confirmed pregnancy), by telephone, fax, or e-mail to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eCRF). Patient confidentiality

must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding safety information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.6.8.2.

8.6.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.6.5 Adverse Events of Special Interest

Not applicable.

8.6.6 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and report as an AE in the eCRF. Details regarding the follow-up of IREs are included in Section 8.6.8.2.

8.6.7 Procedure for Breaking the Blind

This trial does not use blinding procedures.

8.6.8 Follow-up of Adverse Events

8.6.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in the eCRF. For any AE having been identified throughout the trial, or during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).

8.6.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 30 days after the last dose of IMP is administered.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eCRF page and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the

sponsor and recorded on the AE eCRF page and the IRE form, according to the appropriate reporting procedures described in Section 8.6.3.

It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor. The investigator will follow the IREs until:

- the events are resolved,
- the events have stabilized,
- the subject is lost to follow-up, or
- the subject has died.

Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for subjects that become pregnant or for pregnant partners of male subjects.

8.6.8.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the trial intervention(s), should be reported to the sponsor according to the procedures outlined in Section 8.6.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. Any significant follow-up information should continue to be reported to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.7 Treatment of Overdose

There is no experience with OPC-167832 overdose in humans, refer to the IB. For itraconazole and carbamazepine, refer to USPIs

8.8 Subject Assessment Recording

Not applicable.

8.9 Other Assessments

Not applicable.

9 Statistical Considerations

9.1 Sample Size

Sample size was selected assuming an intra-subject coefficient of variation for AUC of 25%, such that the point estimate of the ratio of geometric means for the PK parameters of OPC-167832 with and without coadministration of the perpetrator (itraconazole or carbamazepine) will fall within 83% and 120% of the true value with 90% confidence.

Twenty-four subjects will be enrolled, 12 subjects in each part, to target approximately 10 healthy male or female subjects complete each trial part.

9.2 Datasets for Analysis

The safety dataset includes all subjects who receive at least 1 dose of IMP.

The PK dataset will consist of all subjects who receive at least 1 dose of IMP and have at least 1 postdose evaluable plasma concentration.

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analysis

No data imputation will be performed for missing PK and safety data in this trial.

9.4 Statistical Analyses

9.4.1 Primary Endpoint(s) Analysis

The effect of itraconazole or carbamazepine administration on the single-dose PK of OPC-167832 will be assessed using the primary PK parameters of OPC-167382: Cmax, AUC calculated to the last observable concentration at time t (AUCt), and AUC from time zero to infinity (AUC∞) in the presence and absence of either itraconazole or carbamazepine.

Statistical analyses will be performed using the log-transformed PK parameters. The magnitude of the DDI will be assessed by computing the ratio of the geometric means of OPC-167832 + potentially interacting drug versus OPC-167832 alone and the corresponding 90% confidence intervals (CIs) based on the log-transformed data.

An analysis of variance will be performed on the log-transformed PK parameters C_{max}, AUC_t, and AUC_∞ for OPC-167832 and/or its metabolites using the MIXED procedure in SAS for each part separately. The mixed-effects linear model for each PK parameter will include treatment (OPC-167832 + potentially interacting drug [test] and OPC-167832 alone [reference]) as a fixed effect and subject as a random effect. From each analysis,

mean differences between the treatments OPC-167832 + potentially interacting drug and OPC-167832 alone and the 90% CI for the differences will be derived. The antilog of the differences will then provide an estimate of the geometric mean ratios (GMR; OPC-167832 + potentially interacting drug/OPC-167832 alone), and the antilog of the confidence limits will provide the 90% CIs for the GMRs.

9.4.2 Control of Experiment-wise Type 1 Error

Not applicable.

9.4.3 Safety Analyses

The safety analysis will be conducted on the safety dataset for Part 1 and Part 2, separately. Safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, physical examinations, and the C-SSRS. Summaries will be based upon subjects who took at least 1 dose of IMP. The treatment group refers to OPC-167832 alone and OPC-167832 + itraconazole/carbamazepine. Baseline will be the last available predose value at the start of the treatment period, unless otherwise defined in the statistical analysis plan.

9.4.3.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized by treatment group:

- Treatment-emergent AEs
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

The same summaries will be prepared for TEAEs causally related to the IMP.

9.4.3.2 Clinical Laboratory Data

Descriptive statistics will be used to summarize the change from baseline for laboratory tests by treatment group for each visit. Baseline is defined as the last nonmissing value obtained at a scheduled visit on or before Day −1. If the Day −1 measurement is missing, the baseline value will be the last nonmissing measurement from the screening visit (the previous scheduled visit). The incidence of potentially clinically significant changes and abnormalities in clinical laboratory test parameters will be summarized by treatment group. Clinical laboratory test data will be presented in listings.

9.4.3.3 Physical Examination and Vital Signs Data

Physical examination and vital signs data will be presented in listings.

The change from baseline for vital signs will be summarized by treatment group and visit using descriptive statistics. The incidence of potentially clinically significant values in vital sign parameters will be presented in listings.

9.4.3.4 Electrocardiogram Data

Electrocardiogram data will be presented in listings. The change from baseline in ECG parameters will be summarized by treatment group and visit using descriptive statistics. The incidence of potentially clinically significant changes and abnormalities in ECG evaluations will be summarized.

9.4.3.5 Suicidality Monitoring

The C-SSRS data will be analyzed for evidence of any treatment-emergent issues related to suicidal ideation or behavior. The incidence of suicidality, suicidal behavior, and suicidal ideation will be summarized by treatment group and visit. No inferential statistical analyses will be performed.

9.4.4 Other Analyses

9.4.4.1 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, sex, weight, height, and BMI will be summarized by treatment group using descriptive statistics for Part 1 and Part 2, separately.

9.4.4.2 Pharmacokinetic Analyses

OPC-167832 plasma concentrations will be listed by subject and summarized using descriptive statistics (N, mean, median, standard deviation, percentage coefficient of variation, minimum, and maximum) by treatment and timepoint. The trough plasma concentration of itraconazole, hydroxy-itraconazole, and carbamazepine will be listed by subject and summarized using descriptive statistics, as applicable.

Noncompartmental PK analysis will be performed to estimate the PK parameters for OPC-167832. Values of C_{max}, AUC_t, AUC_∞, time to maximum (peak) plasma concentration (t_{max}), apparent clearance of drug from plasma after extravascular administration (CL/F), body weight normalized CL/F, terminal phase elimination half-life ($t_{1/2,z}$) are planned. Other PK parameters, including those for metabolites, may be reported depending on the concentration data collected. Pharmacokinetic parameters

will be summarized by treatment and timepoint using the same descriptive statistics as for concentrations plus geometric mean. Values of t_{max} will be summarized as median, minimum, and maximum.

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9.5 Interim Analysis and Adaptive Design

No interim analysis or adaptive design are applicable.

9.5.1 Independent Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, Food and Drug Administration (FDA) regulations, applicable ICH Good Clinical Practice (GCP) guidance, international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the eCRF, IRE and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject identifier (ID) will be used to identify each subject.

Financial aspects, subject insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH (International Council for Harmonisation GCP Guidelines, and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB. In support of the site's standard process for administering informed consent, this trial will also allow for eICF as a tool within applicable regions and trial sites. The eICF utilizes the IRB-approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, trial sites will have subjects review and sign the eICF prior to starting any trial procedures; however, if local regulations do not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper and wet ink signature process.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and

documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Prospective trial subjects will be provided with controlled access to the electronic ICF (eICF) application by trial site staff. When the trial site staff and the subject agree that the subject has enough information to make an informed decision to participate, the subject will electronically sign in the eICF application and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF. Any other parties required by the IRB (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the eICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions, the IRB-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the non-subject partner and fetus.

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10.1.3 Recruitment Strategy

Methods for subject recruitment include, but are not limited to: media (ie, television, radio and newspaper), physician referrals, press releases, fliers, random mailings, cold calls and the internet. Methods will be selected before study start.

10.1.4 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior

written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All trial intervention(s), subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject ID in the eCRF. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials, if necessary, subject to local regulations.

10.1.5 Quality Control and Quality Assurance

10.1.5.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the applicable ICH GCP guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.5.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, trial intervention supply, presence of required documents, the informed consent/assent process, site operations, delegation of authority and training, and a review of the eCRF with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.1.6 Protocol Deviations

In the event of a significant/major deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent/assent process, trial intervention dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor or designee at the earliest possible time by telephone or

via e-mail. The investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.7 Records Management

10.1.7.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, progress notes, paper-based assessments and scales, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.7.2 Data Collection

During each subject's visit to the site, an investigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent/assent process, including any revised ICFs;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to trial intervention administration, and confirmation of the subject's actual participation in the trial;
- Documentation of baseline and demographic characteristics (eg, age, weight, BMI, sex, race, ethnicity);
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any significant medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to trial intervention must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and trial intervention compliance;

- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Source documents and source data will be captured electronically (where permitted by local regulation) in this trial and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, accurate, and complete) as paper records. These data will be collected into a system that is fully validated according to 21 CFR Part 11. Changes to the data will be captured by an automatic audit trail.

Designated trial site staff will not be given access to the electronic source system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial site for data collected directly into the application, rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified per the monitoring plan and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or their designee.

Another exception will be safety laboratory [or central ECG data], where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source records will take place; however, on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess trial site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

10.1.7.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with applicable ICH GCP guidance and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Food and Drug Administration regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years after the date on which a New Drug Application is approved by the FDA;
- A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10.1.7.4 Dissemination of Clinical Trial Data

Clinical study reports, periodic safety reports, and clinical trial summary reports will be disclosed after review by regulatory authorities. This includes access to clinical study reports from trials with negative outcomes and from terminated development programs.

10.1.7.5 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other personnel involved in the conduct of the trial who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other personnel involved in the conduct of the trial consent to such acknowledgment in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology: Hemoglobin Hematocrit Mean corpuscular hemoglobin concentration Mean corpuscular volume RBC count WBC count (absolute and differential) Platelets Urinalysis: Specimen appearance Color Occult blood Glucose Microscopic analysis, if indicated, WBC/RBC counts per high powered field pH Protein Specific gravity Additional Tests: Urine or serum pregnancy for females of childbearing potential Follicle-stimulating hormone for postmenopausal females Serology (hepatitis B surface antigen, hepatitis C antibodies, human immunodeficiency virus)	Serum Chemistry: Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bilirubin, total (with reflex if elevated) Blood urea nitrogen Calcium Cholesterol Creatinine Gamma glutamyl transferase Glucose Lactate dehydrogenase Magnesium Potassium Protein, total Sodium Triglycerides Drug Screen (all items in urine except where noted) Alcohol Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Cotinine (urine or serum) Methadone Opiates Phencyclidine Propoxyphene

RBC = red blood cell; WBC = white blood cell.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing potential (FOCBP) are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months). Females of non-childbearing potential do not meet definition of FOCBP.

For males and FOCBP, or their partners, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remain abstinent) to prevent pregnancy during the course of the trial and for 90 days after the last trial intervention administration. Unless the subject is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchiectomy) or remains abstinent during the trial and 90 days after the last trial intervention, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, nonhormonal intrauterine device, birth control pill, birth control implant, birth control depot injection, birth control patch, condom with spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide. Concomitant use of carbamazepine with hormonal contraceptive products (eg, oral and levonorgestrel subdermal implant contraceptives) may render the contraceptives less effective because the plasma concentrations of the hormones may be decreased. Breakthrough bleeding and unintended pregnancies have been reported. For FOCBP enrolled in Part 2 of the trial, if employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, nonhormonal intrauterine device, condom with spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the eCRF or source document. Male subjects must also agree not to donate sperm from trial screening through 90 days after the last trial intervention administration.

Before enrolling males and females in this clinical trial, investigators must review the following information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Contraceptives in current use

- Follow-up of a reported pregnancy

Before trial enrollment, males and FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test for human chorionic gonadotropin will be performed at screening and at check-in to the inpatient facility on all FOCBP. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects must be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives trial intervention(s), the intervention administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the trial intervention(s) and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking trial intervention(s), the intervention(s) must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the trial intervention(s) will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with trial intervention exposure during the trial and for at least 90 days after the last trial intervention administration and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.4 Appendix 4: Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Non-substantial amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of intervention(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent/assent will be obtained from currently enrolled subjects in the trial before the amendment-specified changes in the trial are implemented.

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11 References

1 Otsuka Pharmaceutical Development and Commercialization, Inc. OPC-167832 Investigator's Brochure, Edition 7. Otsuka Report, issued 28 Feb 2022.

2 Yamamura Y. Identification of human cytochrome P450 isoforms involved in metabolism of 14C-OPC-167832 by recombinant human cytochrome P450s. Otsuka Study No. 038119, Otsuka Report No. 031575, 2015.

3 Yamamura Y. Recognition of 14C-OPC-167832 by human P-gp and inhibitory potential of OPC-167832 on quinidine transport in the human P-gp expressing LLC-PK1 cells. Otsuka Study No. 038811, Otsuka Report No. 032277, 2016.

4 Yamamura Y. Recognition of 14C-OPC-167832 by human BCRP and inhibitory potential of OPC-167832 on prazosin transport in the human BCRP expressing MDCKII cells. Otsuka Study No. 039110, Otsuka Report No. 032584, 2017.

5 In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; January 2020.

6 Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Updated 10 Mar 2020. Accessed 04 Apr 2022.

7 Xu Y, Zhou Y, Hayashi M, Shou M, Skiles GL. Simulation of clinical drug-drug interactions from hepatocyte CYP3A4 induction data and its potential utility in trial designs. Drug Metab Dispos. 2011;39(7):1139-1148.

8 United States Department of Health and Human Services, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1. July 2017.

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, OPC-167832, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where , OPC-167832 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eCRF by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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SIGNATURE PAGE

Document Name: 323-201-00007 Study Protocol Amendment 1

Document Number: 1000180384

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