CLINICAL STUDY PROTOCOL

A Phase I, Open-Label Trial to Assess the Mass Balance and Pharmacokinetics of a Single Intravenous Administration of (^{14}C)-OPC-61815 to Healthy Male Japanese Subjects

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Otsuka Pharmaceutical Co., Ltd

Investigational Medicinal Product

(^{14}C)-OPC-61815

REVISED CLINICAL PROTOCOL

A Phase I, Open-Label Trial to Assess the Mass Balance and Pharmacokinetics of a Single Intravenous Administration of (^{14}C)-OPC-61815 to Healthy Male Japanese Subjects

Protocol Lay Person Short Title: A Phase I, Open-Label Trial to Assess the Absorption, Metabolism, and Excretion of (^{14}C)-OPC-61815 in Healthy Male Japanese Subjects

Protocol No. 263-102-00006
EudraCT No. 2019-001968-29

CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	Phase I
Sponsor:	Otsuka Pharmaceutical Co., Ltd 2-9 Kanda-Tsukasamachi Chiyoda-ku Tokyo 101-8535 Japan
Immediately Reportable Event	Otsuka Global Intake E-mail: Global_Intake@otsuka-us.com
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Protocol Summary

1.1 Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd

Name of Investigational Medicinal Product: (^{14}C)-OPC-61815

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Clinical Phase/Trial Type: Phase I

Treatment/Indication: Cardiac edema

Objectives and Endpoints:

Table 1.1-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To determine the mass balance of total radioactivity following a single intravenous (IV) infusion of (^{14}C)-OPC-61815. To determine routes and rates of elimination of total radioactivity following a single IV infusion of (^{14}C)-OPC-61815. To assess the pharmacokinetic (PK) of total radioactivity in plasma and whole blood following a single IV infusion of (^{14}C)-OPC-61815. To assess the PK of OPC-61815 free form and OPC-41061 in plasma following a single IV infusion of (^{14}C)-OPC-61815.	The PK parameter endpoints for OPC-61815 free form and OPC-41061 in plasma, and total radioactivity in whole blood and plasma, and the PK parameter endpoints for total radioactivity in urine and feces are detailed in Section 9.4.3.2.
To identify and characterize metabolites in plasma, urine, and feces following a single IV infusion of (^{14}C)-OPC-61815.	Metabolic profile of (^{14}C)-OPC-61815 and identification of radiolabeled metabolites present at >10% of the total drug-related exposure (AUC) plasma.
Secondary: To assess the safety and tolerability of a single IV infusion of (^{14}C)-OPC-61815.	Adverse events, clinical laboratory evaluations, physical examination findings, vital signs (blood

	pressure, pulse rate), body weight, and 12-lead electrocardiogram parameters.

Trial Design:

Single-site, open-label, nonrandomized, single intravenous (IV) dose trial in healthy male Japanese subjects.

Potential subjects will be screened to assess their eligibility to enter the trial within 28 days prior to the dose administration. Subjects will be enrolled and admitted into the trial site on Day -1. On Day 1, all subjects will receive a single IV infusion of 16 mg containing approximately 75.1 μCi (2.78 MBq) of (^{14}C)-OPC-61815 infused over 60 minutes (55 to 65 minutes, inclusive) in the fasted state.

Subjects will be confined to the trial site until at least Day 9. Subjects will be discharged from the trial site on Day 9 if the following discharge criteria are met:

- ≥ 90% mass balance recovery, and/or
- < 1% of the total radioactive dose is recovered in combined excreta (urine and feces) in 2 consecutive 24-hour periods.

If these criteria are not met by Day 9, subjects will remain at the trial site until any one of the discharge criterion are met up to a maximum of Day 10 to continue 24-hour blood, urine, and feces collections for total radioactivity, unless otherwise agreed upon by the sponsor and investigator.

If criteria are not met by Day 10, subjects may be asked to collect 24-hour excreta samples on up to 2 further occasions on a nonresidential basis to allow extrapolation of urinary and fecal excretion. If needed, the 2 additional 24-hour nonresidential collections will start on Days 10 and 11 (to be brought to the trial site at the end of the collection interval on Days 11 and 12, respectively). If on the second occasion the subject has still not met the desired criterion, then the subject will be discharged from the trial, per investigator and sponsor decision.

Trial Population:

It is planned for at least 8 healthy male Japanese subjects to be dosed to ensure that 6 subjects complete the IV infusion. Up to a maximum of 10 subjects will be dosed in total.

Key Inclusion/Exclusion Criteria:

Key inclusion criteria include but are not limited to the following: Male subjects between 35 and 55 years of age, inclusive; hold a valid Japanese passport and be first-generation

Japanese, defined as the subject, the subject's biological parent, and all of the subject's biological grandparents being of exclusive Japanese descent, have been born in Japan, and not lived outside of Japan for more than 5 years; with a body mass index between 18.5 and 28.0 kg/m^2, inclusive, and a total body weight between 50 and 100 kg, inclusive; in good health, determined by no clinically significant findings from medical history, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening and Check-in as assessed by the investigator (or designee); and have a history of a minimum of 1 bowel movement per day.

Key exclusion criteria include but are not limited to the following: History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion (including cholecystectomy; uncomplicated appendectomy and hernia repair will be allowed); poor peripheral venous access; participation in a clinical trial involving administration of an investigational drug (new chemical entity and/or OPC-61815) in the past 90 days prior to dosing or 5 half-lives of the investigational drug; subjects with exposure to significant diagnostic or therapeutic radiation (eg, serial X-ray, computed tomography scan, barium meal) or current employment in a job requiring radiation exposure monitoring within 12 months prior to Check-in; subjects who have participated in any clinical trial involving a radiolabeled investigational drug within 12 months prior to Check-in.

Trial Site(s): 1 site in the UK

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

(^{14}C)-OPC-61815: Subjects will receive a single IV infusion of 16 mg (^{14}C)-OPC-61815, containing approximately 75.1 μCi (2.78 MBq), over a period of 60 minutes (55 to 65 minutes, inclusive) on Day 1 of the trial.

Trial Assessments:

Assessments for PK: Blood sampling for OPC-61815 free form and OPC-41061 plasma concentrations, whole blood and plasma total radioactivity, and metabolite profiling and identification (plasma). Urine sampling for total radioactivity and metabolite profiling and identification. Feces sampling for measurement of total radioactivity and where possible, metabolite profiling and identification.

Assessments for Safety: Adverse events, clinical laboratory evaluations, physical examination findings, vital signs (supine blood pressure and pulse rate), body weight, and 12-lead ECG.

Screening/Other: demographics, medical history, prior/concomitant medications, urine drug screen, alcohol breath test, serology, oral body temperature, and height.

Data Monitoring Committee: No

Statistical Methods:

Pharmacokinetic parameters will be summarized using descriptive methodology. The following PK parameter endpoints for OPC-61815 free form and OPC-41061 in plasma and total radioactivity in whole blood and plasma will be calculated using standard noncompartmental methods: area under the concentration-time curve (AUC) from time zero to infinity (AUC_∞), AUC calculated to the last observable concentration at time t (AUC_t), maximum peak concentration of the drug (C_{max}), time to maximum peak concentration (t_{max}), time of last measurable (positive) concentration (t_{last}), and terminal-phase elimination half-life ($t_{1/2,z}$). The total body clearance (CL) will also be determined for OPC-61815 free form. The AUC ratios of whole blood total radioactivity relative to plasma total radioactivity (ratios of Blood/Plasma for both AUC_∞ and AUC_t) will be calculated.

The following PK parameter endpoints for total radioactivity in urine will be calculated: amount excreted in urine ($Ae_{,u}$), cumulative $Ae_{,u}$, percentage excreted in urine ($\%fe_{,u}$), and cumulative $\%fe_{,u}$. The following PK parameter endpoints for total radioactivity in feces will be calculated: amount excreted in feces ($Ae_{,f}$), cumulative $Ae_{,f}$, percentage excreted in feces ($\%fe_{,f}$), and cumulative $\%fe_{,f}$. Overall amount and percent of total radioactivity in excreta (combined urine and feces) will be calculated.

No formal statistical analysis will be performed.

Trial Duration:

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

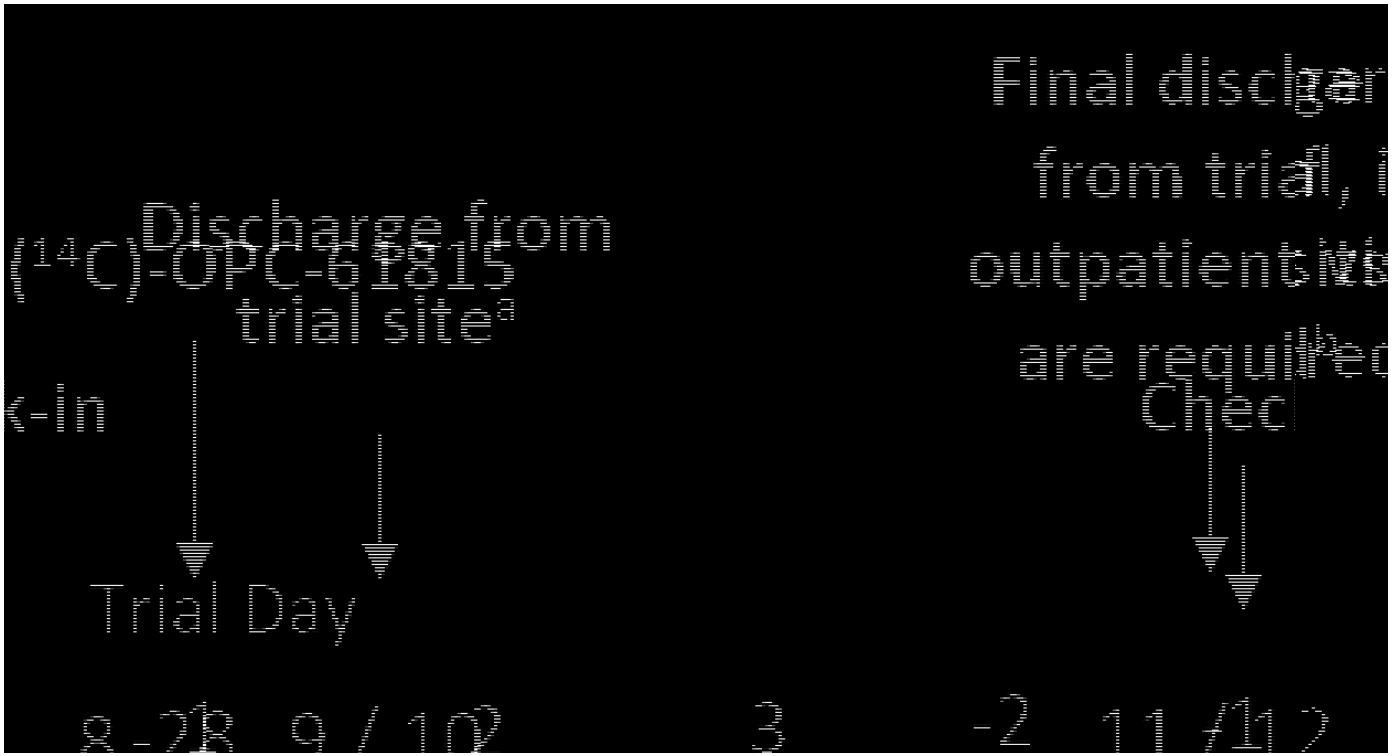
- Screening period (27 days; Day -28 to Day -2)
- Check-in (Day -1)
- Treatment period:
  - Dose administration on Day 1
  - Minimum treatment period duration: 9 days (Day 1 to Day 9)

- Maximum treatment period duration: 12 days (Day 1 to Day 12)
  - Including an outpatient follow-up for 48 hours, if applicable (at investigator's discretion; Day 10 to Day 12)

Final Discharge from trial will be day of discharge from residential treatment period or the day of last outpatient visit if required to attend them based on the discharge criteria.

The total duration of trial participation for each subject (from Screening through Final Discharge from trial) is anticipated to be a maximum of approximately 40 days.

1.2 Schema



[a] Subjects can be discharged on Day 9 if the following discharge criteria are met: ≥ 90% mass balance recovery and/or < 1% of the total radioactive dose is recovered in combined excreta (urine and feces) in 2 consecutive 24-hour periods. If the discharge criteria are not met, subjects will be asked to remain resident within at the trial site and additional 24-hour collection (blood, urine, and feces) for total radioactivity will continue until these criteria are met, up to a maximum of Day 10.

[b] Up to 2 additional 24-hour nonresidential collections (urine and feces) for total radioactivity may occur if discharge criteria have not been met by Day 10. Subjects will collect excreta samples at home for the 24-hour period prior to the clinic visit and deliver them to the trial site at the end of the collection interval, within 24 hours

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Period	Screening Day -28 to Day -2	Check-in Day -1	Days 1 to 8	Discharge[a] Days 9 to 10	Outpatient Visits[b] Days 11 to 12
ENTRANCE/HISTORY					
Informed consent	X				
Demographics	X				
Inclusion/Exclusion Criteria	X	X			
Medical history	X	X[c]			
Urine drug screen	X	X			
Alcohol breath test	X	X			
Serology	X				
Height and body weight	X[d]	X[e]	24 and 48 hours after the start of infusion[e]		
INVESTIGATIONAL MEDICINAL PRODUCT ADMININSTRATION					
(^{14}C)-OPC-61815			Day 1 (0 hours)		
PHARMACOKINETICS					
Blood sampling for OPC-61815 free form and OPC-41061 concentration (plasma)			Predose and 1 hour (end of infusion), and 1.5, 2, 3, 4, 6, 12, 24, and 48 hours after the start of infusion		
Blood sampling for total radioactivity (whole blood and plasma)			Predose and 1 hour (end of infusion), and 1.5, 2, 3, 4, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours after the start of infusion	X[a]	

Table 1.3-1	**Schedule of Assessments**				
Blood sampling for metabolite profiling and identification (plasma)			Predose and 1 hour (end of infusion), and 1.5, 2, 3, 4, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours after the start of infusion		
Urine collection for total radioactivity and metabolite profiling and identification			Predose (from Check-in to 0 hours) and 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, and 144 to 168 hours after the start of infusion	X[a]	X[b]
Feces collection for total radioactivity and metabolite profiling and identification			Predose (from Check-in to 0 hours) and 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, and 144 to 168 hours after the start of infusion	X[a]	X[b]
SAFETY					
Adverse event recording	X	X	Ongoing	X	X
Prior/concomitant medication monitoring	X	X	Ongoing	X	X
Clinical laboratory evaluations	X	X	1.5[i], 24, and 48 hours after start of infusion	X[g]	
Physical examination	X	X[f]	1.5, 24, and 48 hours after start of infusion[f]	X[f, h]	
Supine blood pressure and pulse rate	X	X	1.5, 24, and 48 hours after the start of infusion	X[h]	
Oral body temperature	X				
12-lead electrocardiogram	X	X	24 and 48 hours after the start of infusion	X[g]	

[a] Subjects can be discharged on Day 9 if the following discharge criteria are met: ≥ 90% mass balance recovery and/or < 1% of the total radioactive dose is recovered in combined excreta (urine and feces) in 2 consecutive 24-hour periods. If the discharge criteria are not met, subjects will be asked to remain resident within at the trial site and additional 24-hour collection (blood, urine, and feces) for total radioactivity will continue until these criteria are met, up to a maximum of Day 10.
[b] Up to 2 additional 24-hour nonresidential collections (urine and feces) for total radioactivity may occur if discharge criteria have not been met by Day 10. Subjects will collect excreta samples at home for the 24-hour period prior to the clinic visit and deliver them to the trial site at the end of the collection interval, within 24 hours.
[c] Interim medical history.

[d] Height measured at Screening only.
[e] Weight only.
[f] Symptom-directed physical examination.
[g] Day 9.
[h] Only on day of Discharge.
[i] At this time point only blood samples will be taken for clinical laboratory evaluation.

Table 1.3-2 Time Windows for Assessments

Item	Day	Time point relative to start of infusion (h)	Window
Blood sampling for Pharmacokinetics	1	predose	Within 2 hours of IMP administration
		1	Within 2 minutes after end of IMP administration
		1.5	Specified time point ±2 minutes
		2	Specified time point ±3 minutes
		3	Specified time point ±5 minutes
		4	Specified time point ±10 minutes
		6, 12	Specified time point ±15 minutes
	2	24	Specified time point ±30 minutes
	3	48	Specified time point ±30 minutes
Clinical laboratory evaluations	1	1.5	Specified time point ±10 minutes
	2	24	Specified time point ±120 minutes
	3	48	Specified time point ±120 minutes
Physical examination	1	1.5	Specified time point ±10 minutes
	2	24	Specified time point ±60 minutes
	3	48	Specified time point ±60 minutes
Blood pressure and pulse rate	1	1.5	Specified time point ±10 minutes
	2	24	Specified time point ±60 minutes
	3	48	Specified time point ±60 minutes
Body weight	2	24	Specified time point ±60 minutes
	3	48	Specified time point ±60 minutes
12-lead electrocardiogram	2	24	Specified time point ±60 minutes
	3	48	Specified time point ±60 minutes

Abbreviations: h = hour; IMP = investigational medicinal product.

2 Introduction

OPC-61815 is a compound based on the arginine vasopressin V_2-receptor antagonist tolvaptan (OPC-41061 used henceforth). OPC-41061 was developed as an oral aquaretic agent for the treatment of fluid volume overload conditions and has been approved for the indication of hyponatremia in the US and European countries. OPC-61815 is being developed as an injection formulation, which is expected to provide new clinical benefit in the treatment of hyponatremia and various edematous diseases in patients who have difficulty in swallowing or poor absorption of oral medications.

Please refer to the OPC-61815 Investigator's Brochure (IB)[1] for more detailed information.

2.1 Trial Rationale

The purpose of this trial is to determine the absorption, metabolism, and excretion of (^{14}C)-OPC-61815 and to characterize and determine the metabolites present in plasma, urine, and, where possible, feces in healthy male Japanese subjects following a single intravenous (IV) dose. Knowledge of the absorption, metabolism, and excretion of parent drug and identification/characterization of its metabolites is useful for evaluating the Metabolites in Safety Testing requirements elucidated in the International Conference on Harmonisation M3[2] and the likelihood of effects of renal or hepatic impairment on the disposition of OPC-61815 and the likelihood for drug-drug interactions with OPC-61815.

2.2 Background

OPC-61815 is a compound for which the low water solubility of OPC-41061 has been improved by phosphorylation of the hydroxide of the benzazepine ring. In the body, OPC-61815 is thought to be metabolized to OPC-41061 via hydrolysis of the phosphate ester by alkaline phosphatase and acid phosphatase.

2.3 Summary of Nonclinical Pharmacokinetics

The pharmacokinetics (PK) of OPC-61815 following single IV dosing were investigated in nonfasting rats and dogs. In both species, the plasma concentrations of OPC-61815 (disodium salt [free form]) and its active metabolite OPC-41061 increased dose-dependently. The extrapolated plasma concentration at time zero (C_0) and the area under the concentration-time curve (AUC) from time zero to infinity (AUC_∞) of OPC-61815 (free form) in male rats were both 1.6 times higher than those in female rats. A sex difference in the plasma concentration-time course of OPC-41061 was observed, with the maximum peak concentration of the drug (C_{max}) and AUC_∞ in female rats being respectively 2.4 and 5.8 times higher than those in male rats, indicating a higher plasma

concentration in females. In dogs, the C_0 and AUC_∞ of OPC-61815 (free form) in males were both 0.6 times those in females, while no clear sex difference was observed for OPC-41061. In both species, OPC-41061 was detected in plasma at 5 minutes postdose, indicating rapid hydrolysis from OPC-61815 to OPC-41061.

Following a single IV dose of (^{14}C)-OPC-61815 at 12.75 mg/kg to male rats, radioactivity was distributed into the liver, small intestine, kidney, and adrenal gland at higher levels than the plasma C_{max}. Although, the plasma concentration of radioactivity was lower in female rats than in male rats, no sex differences were observed in the tissue concentrations of radioactivity. At 168 hours postdose, the concentrations of radioactivity were below the lower limit of quantification in almost all tissues. As a result of quantitative autoradiography in pregnant rats, radioactivity concentrations in all fetal tissues were comparable to or lower than the blood concentration in the dams, indicating low transfer of OPC-61815 to fetuses.

The distribution of radioactivity to blood cells was 1.24% to 14.69% in male rats, 1.40% to 26.04% in female rats, and 0.49% to 18.03% in male dogs, indicating low distribution to blood cells in both species.

Following a single IV dose of OPC-61815 to male rats and dogs, in rats, the AUC_∞ of the metabolites DM-4103 and DM-4107 were respectively 1.5 to 4.0 times and 0.17 to 0.62 times that of OPC-41061, and in dogs, the plasma concentrations of DM-4103 and DM-4107 were both lower than that of OPC-41061.

When (^{14}C)-OPC-61815 was incubated with human liver, kidney, lung, and small intestine 9000 g supernatant fractions (S9), OPC-61815 underwent hydrolysis to OPC-41061. OPC-61815 also underwent hydrolysis to OPC-41061 when incubated with human-derived acid phosphatase and alkaline phosphatase. In an investigation of the in vitro metabolism of OPC-61815 by human liver S9 fraction and human hepatocytes, all metabolites detected were the same as those of OPC-41061, and no metabolite with a phosphate group was detected in the metabolic reaction of (^{14}C)-OPC-61815 with human liver S9 fraction.

Following a single IV dose of (^{14}C)-OPC-61815 at 12.75 mg/kg to male and female rats, the urinary and fecal excretion of radioactivity up to 168 hours postdose was 4.59% and 91.08%, respectively, in male rats, and 4.74% and 93.26%, respectively, in female rats, showing that the radioactivity administered was excreted mainly in feces. The biliary excretion of radioactivity was 92.2% in male rats and 91.5% in female rats. In male rats, 61.0% of the radioactivity administered was resorbed via enterohepatic circulation. No obvious sex difference was noted in urinary, fecal, or biliary excretion in rats. Following

a single IV dose of (^{14}C)-OPC-61815 at 3.825 mg/kg to male dogs, the urinary and fecal excretion of radioactivity up to 168 hours postdose was 5.32% and 89.50%, respectively.

2.4 Summary of Clinical Experience

2.4.1 Safety

In a Phase I single IV dose trial in healthy male adults (protocol No.: 263-08-001), OPC-61815 at 0.3, 1, 3, 7.5, 15, or 30 mg or placebo was administered intravenously over 5 minutes to 54 subjects. Twenty-four adverse events (AEs) occurred in 13 of 36 subjects (36.1%) in the OPC-61815 group, and 12 AEs occurred in 5 of 18 subjects (27.8%) in the placebo group. The AEs that occurred in at least 2 subjects in the OPC-61815 group were 2 occurrences each of ventricular extrasystoles, abdominal pain, and blood cholesterol increased. Of these all but 1 case of abdominal pain, were considered to be potentially drug-related treatment-emergent AEs (TEAEs). All AEs in this trial were mild in severity and resolved with or without treatment. The above results demonstrated that a single IV dose of OPC-61815 at 0.3 to 30 mg is well-tolerated in healthy male adults.

In a Phase I multiple IV dose trial in healthy male adults (protocol No.: 263-09-001), OPC-61815 at 1.25, 5, or 20 mg or placebo was administered intravenously over 1 minute to 36 subjects. After receiving a single dose, subjects were given a 1-day dose intermission and then received multiple once-daily IV doses for 7 days. In total, 168 AEs occurred in 24 of 27 subjects (88.9%) in the OPC-61815 group and 5 AEs occurred in 4 of 9 subjects (44.4%) in the placebo group. The AEs reported in at least 3 subjects in the OPC-61815 group were as follows: 39 occurrences of feeling abnormal in 9 subjects, 31 occurrences of pruritus in 5 subjects, 5 occurrences of blood uric acid increased in 5 subjects, 4 occurrences of diarrhoea in 4 subjects, 24 occurrences of pruritus generalized in 3 subjects, 8 occurrences of erythema in 3 subjects, and 4 occurrences of bradycardia in 3 subjects. Of these events, 38 occurrences of feeling abnormal in 8 subjects, 5 occurrences of blood uric acid increased in 5 subjects, 30 occurrences of pruritus in 4 subjects, 24 occurrences of pruritus generalized in 3 subjects, 8 occurrences of erythema in 3 subjects, 16 occurrences of hypoesthesia in 2 subjects, 2 occurrences of diarrhea in 2 subjects, 9 occurrences of nausea in 2 subjects, and 7 occurrences of pruritus genital in 1 subject were judged to be potentially drug-related TEAEs. No deaths or other serious potentially drug-related TEAEs were observed. All AEs reported in the OPC-61815 group were mild or moderate in severity and resolved without treatment. The results demonstrated that OPC-61815 is well-tolerated in healthy male adults when administered intravenously once daily for 7 days at up to 20 mg. However, based on the fact that potentially drug-related TEAEs that did not occur after oral administration of OPC-41061, such as feeling abnormal, pruritus, and erythema, occurred with a high

incidence during or immediately after repeated administration of OPC-61815; OPC-61815 solution was suspected to be involved in the occurrence of such potentially drug-related TEAEs.

In order to explore causes of the potentially drug-related TEAEs and explore the injection duration able to reduce the occurrence of these potentially drug-related TEAEs, a Phase I IV infusion rate trial (protocol No.: 263-10-005) was conducted. A single dose of OPC-61815 at 7.5 or 15 mg or placebo was administered intravenously over 2 hours, 5 minutes, or 1 minute to healthy male adult subjects. Adverse events occurred in 6 of 12 subjects in the OPC-61815 group and 5 of 6 subjects in the placebo group after administration over 2 hours; 10 of 12 subjects in the OPC-61815 group and 3 of 6 subjects in the placebo group after administration over 5 minutes; and 10 of 12 subjects in the OPC-61815 group and 4 of 6 subjects in the placebo group after administration over 1 minute. All the AEs reported were mild or moderate in severity. Adverse events (feeling abnormal, feeling hot, erythema, hyperhidrosis, pruritus, rash, urticaria, nausea, epigastric discomfort, and dyspnea) similar to feeling abnormal, pruritus, or erythema, which occurred with a high incidence in the multiple IV dose trial of OPC-61815 (protocol No.: 263-09-001) were extracted as AEs of special interest (AESI). Adverse events of special interest were reported in 1 of 12 subjects in the OPC-61815 group and 3 of 6 subjects in the placebo group after administration over 2 hours (pruritus, rash, urticaria, and feeling abnormal). A relationship to the trial drug was ruled out for AEs that occurred in 1 subject (rash) in the OPC-61815 group and 2 subjects in the placebo group (feeling abnormal and urticaria), out of the above AEs. After administration over 5 minutes, AESIs were reported in 9 of 12 subjects in the OPC-61815 group and 2 of 6 subjects in the placebo group (dyspnea, erythema, hyperhidrosis, pruritus, feeling abnormal, and feeling hot). All these AEs were assessed as related to the trial drug. After administration over 1 minute, AESIs were reported in 10 of 11 subjects in the OPC-61815 group and 4 of 6 subjects in the placebo group (nausea, epigastric discomfort, erythema, hyperhidrosis, pruritus, feeling abnormal, and feeling hot). All these AEs, except for 1 event (erythema) in the OPC-61815 group, were assessed as related to the trial drug. All potentially drug-related TEAEs occurred during or immediately after IV dosing, and most of them resolved without treatment within 10 minutes of the start of trial drug administration. There were no clinically significant changes from baseline in plasma histamine concentration. As shown above, causes of AESIs remained unknown.

2.4.2 Pharmacokinetics

Pharmacokinetic data for OPC-61815 free form following single and multiple IV doses is presented in the table below. The PK data for OPC-61815 free form following 1- and 5-minute infusions is available in the IB[1], along with PK data for OPC-41061 and major metabolites for all studies.

Table 2.4.2-1 Pharmacokinetic Data for OPC-61815 Free Form

Dose (mg)	AUC_∞ (ng.h/mL)	AUC_t (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)
Single IV dose – Mean (SD)					
0.3 mg	-	7.803 (8.170)	53.02 (29.28)	0.020 (0-0.25)	-
1 mg	175.0 (-)	85.90 (21.91)	182.2 (21.72)	0.000 (0-0.25)	0.7170 (0-0)
3 mg	427.2 (61.14)	374.3 (52.91)	559.5 (85.52)	0.000 (0-0.02)	0.6335 (0.1065)
7.5 mg	1242 (182.2)	1144 (171.1)	1832 (294.2)	0 (0-0)	1.172 (0.2819)
15 mg	3008 (416.6)	2868 (362.3)	3348 (637.7)	0.000 (0-0.25)	1.730 (0.3279)
30 mg	4882 (817.9)	4727 (839.9)	7670 (755.3)	0 (0-0)	1.683 (0.4837)
Multiple IV dose – Day 1: Mean (SD)					
1.25 mg	211.8 (32.11)	167.3 (32.55)	371.8 (78.15)	3.0 (3-3)	0.5308 (0.1074)
5 mg	886.7 (140.8)	784.0 (150.2)	1165 (394.4)	3.0 (3-15)	1.193 (0.3741)
20 mg	3379 (492.8)	3178 (400.1)	4351 (1496)	3.0 (3-15)	2.510 (1.927)
Multiple IV dose – Day 9: Mean (SD)					
1.25 mg	169.0 (33.05)[b]	-	320.0 (89.42)	3.0 (3-15)	0.5748 (0.1549)
5 mg	924.8 (136.9)[b]	-	1375 (368.4)	3.0 (3-3)	1.329 (0.4530)
20 mg	3416 (344.7)[b]	-	4137 (955.7)	3.0 (3-15)	2.419 (1.145)

Abbreviations: 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; AUC_{24h} = area under the concentration-time curve from time zero until 24 hours postdose; C_{max} = maximum peak concentration; IV = intravenous; t_{max} = time to maximum peak concentration; $t_{1/2}$ = elimination half-life.
[a] median (min-max)
[b] AUC_{24h}

2.5 Known and Potential Risks and Benefits

Healthy subjects in the current trial will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the trial. The risks of participation are primarily those associated with adverse reactions to the trial treatment

and the IV doses, although there may also be some discomfort from collection of blood samples and other trial procedures.

No deaths or other serious adverse events (SAEs) were reported in the Phase I trials of OPC-61815 in healthy adult male subjects (263-08-001, 263-09-001, and 263-10-005). Feeling abnormal, feeling hot, erythema, hyperhidrosis, pruritus, rash, urticaria, nausea, epigastric discomfort, and dyspnea were frequently reported following IV dosing of OPC-61815 in Trials 263-09-001 and 263-10-005, and were considered AESIs. In Trial 263-10-005, 1- and 5-minute administrations were associated with frequent occurrences of AESIs in OPC-61815-treated subjects, whereas following a 2-hour administration, only 1 subject experienced an AESI, and this was considered unrelated to trial drug. These findings suggest that a longer duration of OPC-61815 administration would reduce the risk of developing these events.

All potentially trial drug-related AEs reported in completed Phase I trials occurred during or immediately after trial drug administration. Most events spontaneously resolved within 10 minutes after start of trial drug administration, subjects should be closely monitored for skin symptoms following start of trial drug administration.

More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with OPC-61815 may be found in the IB.[1]

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

3 Objectives and Endpoints

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To determine the mass balance of total radioactivity following a single IV infusion of (^{14}C)-OPC-61815. To determine routes and rates of elimination of total radioactivity following a single IV infusion of (^{14}C)-OPC-61815. To assess the PK of total radioactivity in plasma and whole blood following a single IV infusion of (^{14}C)-OPC-61815.	The PK parameter endpoints for OPC-61815 free form and OPC-41061 in plasma, and total radioactivity in whole blood and plasma, and the PK parameter endpoints for total radioactivity in urine and feces are detailed in Section 9.4.3.2.

To assess the PK of OPC-61815 free form and OPC-41061 in plasma following a single IV infusion of (^{14}C)-OPC-61815. To identify and characterize metabolites in plasma, urine, and feces following a single IV infusion of (^{14}C)-OPC-61815.	Metabolic profile of (^{14}C)-OPC-61815 and identification of radiolabeled metabolites present at >10% of the total drug-related exposure (AUC) plasma.
Secondary: To assess the safety and tolerability of a single IV infusion of (^{14}C)-OPC-61815.	Adverse events, clinical laboratory evaluations, physical examination findings, vital signs (blood pressure, pulse rate), body weight, and 12-lead electrocardiogram parameters.

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This will be a Phase I, single-site, open-label, nonrandomized, single IV dose trial in healthy male Japanese subjects.

Potential subjects will be screened to assess their eligibility to enter the trial within 28 days prior to the dose administration. Subjects will be enrolled and admitted into the trial site on Day -1. On Day 1, all subjects will receive a single IV infusion of 16 mg (^{14}C)-OPC-61815, containing approximately 75.1 µCi (2.78 MBq), over 60 minutes (55 to 65 minutes, inclusive) in the fasted state.

It is planned for at least 8 subjects to be dosed to ensure that 6 subjects complete the IV infusion. Up to a maximum of 10 subjects will be dosed in total.

An overview of the trial design is shown in Figure 1.2-1.

Subjects will be confined to the trial site until at least Day 9. Subjects will be discharged from the trial site on Day 9 if the following discharge criteria are met:

- ≥ 90% mass balance recovery, and/or
- < 1% of the total radioactive dose is recovered in combined excreta (urine and feces) in 2 consecutive 24-hour periods.

If these criteria are not met by Day 9, subjects will remain at the trial site until any one of the discharge criterion are met up to a maximum of Day 10 to continue 24-hour blood,

urine, and feces collections for total radioactivity, unless otherwise agreed upon by the sponsor and investigator.

If criteria are not met by Day 10, subjects may be asked to collect 24-hour excreta samples on up to 2 further occasions on a nonresidential basis to allow extrapolation of urinary and fecal excretion. If needed, the 2 additional 24-hour nonresidential collections will start on Days 10 and 11 (to be brought to the trial site at the end of the collection interval on Days 11 and 12, respectively). If on the second occasion the subject has still not met the desired criterion, then the subject will be discharged from the trial, per investigator and sponsor decision.

Final Discharge from trial will be day of discharge from residential treatment period or the day of last outpatient visit if required to attend them based on the discharge criteria. The total duration of trial participation for each subject (from Screening through Final Discharge from trial) is anticipated to be a maximum of approximately 40 days.

The start of the trial is defined as the date the first enrolled subject signs an informed consent form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of trial is defined as the last date of contact or the date of final contact attempt for the last subject completing or withdrawing from the trial.

A Schedule of Assessments is presented in Table 1.3-1 (Section 1.3).

4.2 Scientific Rationale for Trial Design

This trial will be open-label because the primary endpoints of the trial are considered objective. Conducting the trial in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Subjects over 35 years of age will be used to minimize the risk to fertility in healthy subjects. Japanese subjects are to be recruited with a view to possibly submitting a marketing application for OPC-61815 in Japan in the future.

Female subjects will be excluded to align with regulatory guidance. The “as low as (is) reasonably achievable” (ALARA) principle prescribed by the International Commission in Radiological Protection (ICRP)[3] recommends that radiation exposure to subjects should be kept ALARA; therefore, if no specific reason exists to include females (ie, no available data suggest metabolism of the trial drug is different in females versus males), then the radiation exposure to female subjects should ideally be kept at zero by not including females in this radioactivity trial and only enrolling and dosing male subjects.

The duration of the IV infusion was selected to minimize the risk of frequently observed TEAEs including feeling abnormal, pruritus, and erythema during the trial; and it is

planned for at least 8 subjects to be dosed to ensure that 6 subjects complete the IV infusion, with up to a maximum of 10 subjects being dosed in total.

4.3 Dosing Rationale

A single dose level of 16 mg, containing approximately 75.1 µCi (2.78 MBq) of (^{14}C)-OPC-61815, will be administered to each subject. This equates to a radioactivity exposure of approximately 1 mSv. The radioactive dose is an acceptable dose to give to healthy subjects and is considered adequate to define the disposition of (^{14}C)-OPC-61815.

The committed effective radiation doses to be administered have been calculated by Public Health England's (PHE) Centre for Radiation, Chemical, and Environmental Hazards, based on the results of a preclinical mass balance trial and a quantitative whole body autoradiography trial.[4] The effective radiation dose is defined as being within dose limits for members of the public (Category II trial, World Health Organization)[5] with a minor associated risk (risk Category IIa, ICRP).[3]

In order to provide the optimal conditions for the objectives of the trial to be met, the radioactive dose considered for administration will be reviewed following calculation by PHE, together with any bioanalytical data from the preclinical species to ensure radioactivity concentrations in urine, feces, and plasma are detectable for sufficient periods postdose.

Intravenous administration was chosen since this is the intended clinical route of administration. Based on the nonclinical data and the known PK of OPC-61815, the sample collection timing and duration of this trial are considered adequate to achieve the trial objectives.

A 16-mg dose of (^{14}C)-OPC-61815 is within the anticipated clinical dose range and is considered to be high enough to fully characterize the single IV dose PK of the parent compound.

4.4 End of Trial Definition

The end of trial date is defined as the last date of contact or the date of final contact attempt 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 was administered the complete dose of the IMP. For purposes of this trial, subjects who complete Final Discharge from the trial will be defined as trial completers.

5 Trial Population

It is planned for at least 8 healthy male Japanese subjects to be dosed to ensure that 6 subjects complete the IV infusion. Up to a maximum of 10 subjects will be dosed in total.

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). Site number will be designated by the sponsor. The subject number will be given sequentially from S00001.

Demographic information (collection date, year of birth, age, sex, race, ethnicity, country) and medical history will be recorded in eCRF at 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 all of the following criteria at the Screening visits, unless otherwise stated:

1) Male subjects between 35 and 55 years of age, inclusive.
2) Hold a valid Japanese passport and be first-generation Japanese, defined as the subject, the subject's biological parent, and all of the subject's biological grandparents being of exclusive Japanese descent, have been born in Japan, and not lived outside of Japan for more than 5 years.
3) Body mass index between 18.5 to 28.0 kg/m^2 (inclusive); and a total body weight between 50 and 100 kg, inclusive.
4) In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital sign measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening and Check-in as assessed by the investigator (or designee).
5) Subjects will agree to use contraception as detailed in Section 10.4.
6) Able to comprehend and willing to sign an ICF and to abide by the trial restrictions.
7) History of a minimum of 1 bowel movement per day.

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at the Screening visit, unless otherwise stated:

1) Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator (or designee).
2) History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee).
3) History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion (including cholecystectomy; uncomplicated appendectomy and hernia repair will be allowed).
4) Abnormal laboratory values at Screening or Check-in, as confirmed by repeat, including the following:
    a) Alanine aminotransferase (ALT) level above 1.5 x upper limit of normal (ULN)
    b) Aspartate aminotransferase (AST) level above 1.5 x ULN
    c) Total bilirubin level above 1.5 x ULN
5) History of alcoholism or drug/chemical abuse within 2 years prior to Check-in.
6) Alcohol consumption of >14 units per week for males. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
7) Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
8) Positive hepatitis panel and/or positive human immunodeficiency virus test.
9) Participation in a clinical trial involving administration of an investigational drug (new chemical entity and/or OPC-61815) in the past 90 days prior to dosing or 5 half-lives of the investigational drug.
10) Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the investigator (or designee).
11) Use or intend to use any prescription medications/products within 30 days prior to Check-in, unless deemed acceptable by the investigator (or designee).
12) Use or intend to use slow-release medications/products considered to still be active within 30 days prior to Check-in, unless deemed acceptable by the investigator (or designee).

13) Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 14 days prior to Check-in, unless deemed acceptable by the investigator (or designee).
14) Use of tobacco- or nicotine-containing products within 3 months prior to Check-in, or positive cotinine at Screening or Check-in.
15) Receipt of blood products within 2 months prior to Check-in.
16) Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening; or plans to donate blood within 2 months of trial completion.
17) Poor peripheral venous access.
18) Subjects with exposure to significant diagnostic or therapeutic radiation (eg, serial X-ray, computed tomography scan, barium meal) or current employment in a job requiring radiation exposure monitoring within 12 months prior to Check-in.
19) Subjects who have participated in any clinical trial involving a radiolabeled investigational drug within 12 months prior to Check-in.
20) Subjects who, in the opinion of the investigator (or designee), should not participate in this trial.

Contraceptive guidance and collection of pregnancy information can be found in Section 10.4.

Subjects must agree to restrictions to medications and lifestyle described in Section 6.5.1 and Section 5.3, respectively.

5.3 Lifestyle Considerations/Trial Restrictions

The following lifestyle considerations apply for the trial:

- Subjects should refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior Screening, or platelets from 6 weeks prior to Screening; or plans to donate blood within 2 months of Final Discharge from trial.
- Subjects should not have received blood products within 2 months prior to Check-in.
- Subjects should follow contraception guidance as detailed in Section 10.4.

5.3.1 Meals and Dietary Restrictions

While confined at the trial site, subjects will receive a standardized, high-fiber diet at scheduled times that do not conflict with other trial-related activities. Prune juice may be administered on an as-needed basis to aid in normal bowel function and will not be considered a concomitant medication. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

Foods and beverages containing poppy seeds, grapefruit, star fruit, or Seville oranges will not be allowed from 7 days prior to Check-in until Final Discharge from trial.

5.3.2 Caffeine, Alcohol, and Tobacco

Caffeine-containing foods and beverages will not be allowed from 36 hours before Check-in until Final Discharge from trial.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until Final Discharge from trial.

Use of tobacco- or nicotine-containing products will not be permitted from 3 months prior to Check-in until Final Discharge from trial.

Information regarding the subject's alcohol, caffeine, and smoking habits will be documented in the subject's eCRF. The collection dates and results of the alcohol breath test and cotinine test for smoking will be documented in the subject's eCRF.

5.3.3 Activity

Subjects are required to refrain from strenuous exercise from 7 days before Check-in until Final Discharge from trial and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

5.4 Screen Failures

Subjects who sign an ICF but who are not started on treatment are permitted to be re-screened. In the event that the subject is re-screened for trial participation, and the re-screening is not completed within the original Screening window, a new ICF must be signed.

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who does not receive trial treatment.

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

- Date of informed consent
- Visit date (Screening visit)
- Demographics (collection date, year of birth, age, sex, race, ethnicity, country)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure

6 Trial Treatments

6.1 Trial Treatments Administered

Subjects will receive a single IV infusion of 16 mg (^{14}C)-OPC-61815, containing approximately 75.1 µCi (2.78 MBq), over a period of 60 minutes (55 to 65 minutes, inclusive) on Day 1 of the trial.

Subjects may be asked to be supine for the IV infusion. The subject's start and end time of infusion will be documented in the source data and eCRF. If the infusion is interrupted, the time (start and end of interruption) for each interruption, reason for interruption, if the administration was temporarily suspended and resumed, and if the full dose was administered will be documented in the subject's source documents and eCRF.

Subjects will be dosed in numerical order.

For information regarding the criteria required to be met for subject discharge, see Section 4.1.

6.1.1 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the Pharmacy Manual.

6.2.1 Packaging and Labeling

Active pharmaceutical ingredient (API; nonradiolabeled powder) will be supplied by the sponsor. Arcinova will synthesize the radiolabeled API (powder) and dilute this to the correct specific radioactivity with the nonradiolabeled API. Covance will manufacture and label the IMP, such that each unit dose contains a total of 16 mg OPC-61815 containing approximately 75.1 µCi (2.78 MBq) of (^{14}C).

Each vial of IMP used will be labeled to clearly disclose the subject number, compound ID, batch/lot numbers, the storage conditions, for clinical trial use only, protocol number, sponsor/trial site name and address, instructions for use, route of administration, and appropriate precautionary statements, and any other information required by local regulatory authorities.

Arcinova will provide a Certificate of Analysis for the radiolabeled API and Covance will provide a Certificate of Analysis for the IMP. A Certificate of Release authorized by a Qualified Person in the European Union will also be issued, by a Covance Qualified Person, for the IMP prior to administration to subjects.

6.2.2 Storage

The IMP will be stored according to the instructions on the label at the trial site in a location that is locked with restricted access.

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 received, dispensed, administered, and returned. Neither the investigator nor any designees may provide IMP to any subject not participating in this protocol. This drug accountability record will be available for inspection at any time. At the completion of the trial, the original drug accountability record will be available for review by the sponsor upon request.

The Pharmacy Manual will detail the procedure for determining residual radioactivity in the equipment used for IV infusions. Any unused assembled unit doses will be retained until completion of the trial.

6.2.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially used IMP will be disposed of after confirmation with the sponsor.

6.2.5 Reporting of Product Quality Complaints

A product quality complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate, or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness, or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP 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) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

For any PQC, please contact the Covance Pharmacy Manager (+44 [0]113 301 3519). If Covance receive a PQC by telephone, then information will be provided to sponsor by e-mail (PQC_263-102-00006@otsuka.jp).

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, telephone 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 (if available)
- Availability for return

6.2.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in a packaging specified by the sponsor.

It must be documented in the site accountability record that a 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 or its designee.

6.2.6 Investigational Medicinal Product Reserve Sample Requirements

Not applicable.

6.3 Measures to Minimize/Avoid Bias

This is an open-label trial.

6.4 Subject Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified trial site staff.
- A predose and postdose inventory of IMP will be performed.

6.5 Concomitant Medications or Therapies

The investigator will record all medications and therapies taken by the subject from 6 weeks prior to signing of informed consent through the end of the treatment period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) on 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) on 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

As described in the exclusion criteria (Section 5.2.2), subjects are prohibited from use of any prescription and/or nonprescription medications/products (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations; medications/products known to alter drug absorption; metabolism, or elimination processes, slow-release medications/products considered active within 30 days prior to Check-in) for varying times prior to Check-in.

None of the medications specified below, excluding the planned IMP, are allowed to be taken for the following periods throughout the trial, unless the investigator (or designee) and/or sponsor have given their prior consent:

- The use of any medications/products know to alter drug absorption, metabolism, or elimination processes, including St. John’s wort, is prohibited within 30 days prior to Check-in until Final Discharge from trial.
- The use of any prescription medications/products is prohibited within 30 days prior to Check-in until Final Discharge from trial.
- The use of any slow-release medications/products considered to still be active is prohibited within 30 days prior to Check-in until Final Discharge from trial.

- The use of nonprescription medications/products, including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations, is prohibited within 14 days prior to Check-in until Final Discharge from trial.

Restrictions/prohibitions on the intake of products, food, beverages, containing grapefruit, Seville orange, or star fruit due to OPC-41061 and its metabolites being metabolized mainly by CYP3A4 are detailed in Section 5.3.1.

The administration of any other concomitant medications during the trial is prohibited without prior approval of the investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the trial and the reason for its use will be documented in the source data and eCRF.

6.5.2 Rescue Medication

Not applicable.

6.6 Intervention After the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

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

The trial may be discontinued at the discretion of the investigator (or designee), sponsor, or medical monitor if any of the following criteria are met:

- Adverse events unknown to date (ie, not previously reported in any similar investigational drug trial with respect to their nature, severity, and/or duration)
- Increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of subjects
- Cancelation of drug development.

7.2 Individual Site

Trial site participation may be discontinued by the sponsor, the investigator, or the EC, if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent

with applicable laws, regulations, and Good Clinical Practice (GCP). The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the EC at the site.

7.3 Treatment Interruption

During the IV infusion all subjects should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that a significant infusion reaction occurs, if the investigator determines necessary, supportive care should be employed in accordance with the symptoms/signs.

If the infusion is interrupted: the start and end time for each interruption, reason for interruption, if the administration was temporarily suspended and resumed, and if the full dose was administered, will be documented in the subject's source documents and eCRF.

7.4 Individual Subject Discontinuation

7.4.1 Treatment Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AE, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator.

If a subject is withdrawn from trial, the sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's eCRF. If a subject is withdrawn, efforts will be made to perform all discharge assessments, if possible (Table 1.3-1). Other procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the investigator (or designee) to have stabilized.

Subjects who do not complete the IV infusion of (^{14}C)-OPC-61815 may be replaced, with up to a maximum of 10 subjects being dosed in total.

7.4.2 Documenting Reasons for Treatment Discontinuation

A subject may discontinue the trial or be withdrawn from the trial for the reasons listed below:

- Adverse event
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE, which is not otherwise determined to be an undue hazard
  - Continuing infusion of the 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
- Physician decision
- Protocol deviation
- Site terminated by sponsor
- Trial terminated by sponsor
- Withdrawal by subject
- Other

If the subject discontinues the trial due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.4.1 must be followed.

7.4.3 Withdrawal of Consent or Assent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

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 an in-home visit).
- Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).

- Contact of the subject by trial personnel, 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, vital registries, or 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 IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.4.1). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should follow the instructions outlined in Section 7.4.2 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or Schedule of Assessments can be accommodated. 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.

7.4.4 Procedures to Encourage Continued Trial Participation

Not applicable.

7.5 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Final Discharge from trial, who do not have a known reason for discontinuation (eg, withdrew consent 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 for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for 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," "Were you able to contact the subject?," "Date of contact/Date of final contact attempt," and "Contact method" will be recorded in the subject's eCRF.

8 Trial Procedures

The assessments to be conducted during the trial are summarized in Section 1.3_Schedule_of_Assessments.

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same time point.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a time point is (in descending order of priority):

- dosing
- blood samples
- urine and feces collections for PK assessments
- any other procedures (ECGs will be scheduled before vital signs measurements).

Where activities at a given time point coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, blood draws.

8.1 Efficacy Assessments

Not applicable.

8.2 Pharmacokinetic Assessments

8.2.1 Pharmacokinetic Blood/Plasma Samples

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Table 1.3-1) for determination of OPC-61815 free form and OPC-41061 concentrations, total radioactivity, and metabolite profiling and identification. Blood samples will be collected from the contralateral arm to the arm/hand used for dose administration.

Blood samples will be collected in vacutainers containing K2EDTA and processed into plasma. Approximately 1 × 2 mL blood sample will be collected for total radioactivity in whole blood and approximately 1 × 5 mL blood sample will be collected for total radioactivity in plasma. Approximately 1 × 3 mL blood sample will be collected for OPC-61815 free form and OPC-41061 concentrations in plasma. Approximately 1 × 10 mL blood sample will be collected for metabolite profiling and identification in plasma.

Procedures for collection, processing, and shipping of blood samples will be detailed in a separate document. If any unknown metabolites are detected and further investigation is necessary, a part of the plasma samples will be shipped on dry ice to the sponsor (Otsuka Pharmaceutical Co., Ltd., Tokushima Research Institute) and used for the structure elucidation of unknown metabolites, which will be conducted separately. The investigation of these unknown metabolites will be reported separately, and the report will not be appended to the clinical study report.

The dates and times of blood collections will be documented in the subject's eCRF.

8.2.2 Pharmacokinetic Urine and Feces Samples

Urine will be collected over the time intervals indicated in the Schedule of Assessments (Table 1.3-1) for determination of total radioactivity and metabolite profiling and identification.

Feces will be collected over the time intervals indicated in the Schedule of Assessments (Table 1.3-1) for determination of total radioactivity, and, where possible, metabolite profiling and identification. If possible, a single baseline fecal sample will be collected from after Check-in on Day -1 until just prior to dose administration on Day 1.

Procedures for collection, processing, and shipping of urine and fecal collections will be detailed in a separate document. If any unknown metabolites are detected and further investigation is necessary, a part of the urine samples and/or extracted feces samples will be shipped on dry ice to the sponsor (Otsuka Pharmaceutical Co., Ltd., Tokushima Research Institute) and used for the structure elucidation of unknown metabolites, which will be conducted separately. The investigation of these unknown metabolites will be reported separately, and the report will not be appended to the clinical study report.

The start and end dates and times of each urine collection time point interval and the total volume of urine collected in each time point interval will be documented in the subject's eCRF. The start and end dates and times of each fecal collection time point interval and the total weight of the collected fecal samples for each time point interval will be documented in the subject's eCRF.

8.2.3 Analytical Methodology

Plasma concentrations of OPC-61815 free form and OPC-41061 will be determined using a validated analytical procedure. Whole blood, plasma, urine, and feces total radioactivity will be determined with liquid scintillation counting. Profiling and identification of metabolites in plasma, urine, and, where possible, feces will be conducted using standard laboratory procedures.

8.3 Pharmacodynamic Assessments

Not applicable.

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Biomarker Assessments

Not applicable.

8.6 Future Biospecimen Research Samples

Not applicable.

8.7 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8.

8.7.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the Schedule of Assessments (Table 1.3-1) to perform the clinical laboratory evaluations described in Section 10.2.

For assessment of hematology and serum chemistry, 7.5 mL of blood will be required at each time point (Table 1.3-1), and for assessment of serology (Screening only; Table 1.3-1), 3.5 mL of blood will be required.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments (Table 1.3-1). An investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

The dates and times of collections for clinical laboratory evaluations will be documented in the subject's eCRF. The results of the drugs of abuse screen, cotinine test, and alcohol breath test at Screening and/or Check-in will be documented in the subject's eCRF.

8.7.2 Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the time points as specified in the Schedule of Assessments (Table 1.3-1).

The dates, times, and results of the physical examinations will be documented in the subject's eCRF.

8.7.3 Vital Signs

Supine blood pressure, supine pulse rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments (Table 1.3-1). Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly, and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

The dates, times, and results of the vital sign measurements (supine blood pressure, supine pulse rate, and oral body temperature) will be documented in the subject's eCRF.

8.7.4 Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments (Table 1.3-1).

Single 12-lead ECGs will be performed singly, and repeated once if the Investigator deems a repeat is indicated.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

The dates, times, and results of the 12-lead ECG (PR interval, QRS, QT-interval, and QT interval corrected for heart rate using Fridericia's formula) will be documented in the subject's eCRF.

8.7.5 Suicidality Monitoring

Not applicable.

8.7.6 Other Safety Variables

Weight will be assessed at the times indicated in the Schedule of Assessments (Table 1.3-1). The date, time, and weight will be documented in the subject's eCRF at each scheduled time point.

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. 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 an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE.

Treatment-emergent AEs are defined as AEs with an onset date on or after the start of open-label treatment. In more detail, TEAEs are all AEs which started after start of open-label IMP treatment; or if the event was continuous from pre-IMP treatment and was worsening, serious, IMP-related, or resulted in death, discontinuation, interruption, or reduction of IMP.

An 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.

- 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: A noteworthy event for the particular product/IMP or class of products that a sponsor may wish to monitor carefully. All AESIs are to be reported as immediately reportable events (IREs).

Immediately Reportable Event:

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 8.8.6).
- Pregnancy in a female partner of a male subject are also defined as IREs. Although this will only occur in a female partner of a male subject, it must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication. This includes pregnancy of the partner of the subject.

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 on 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.

8.8.2 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?." Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the trial to the investigator (or designee).

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 signs the ICF to Final Discharge from the trial.

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.

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 8.8.3. Special attention should be paid to recording hospitalization and concomitant medications.

Adverse event, start date, end date (if possible, start date and time, end date and time), seriousness, severity, relationship to trial treatment (IMP Causality), action taken with trial treatment and outcome will be recorded on the source documents and in the eCRF.

8.8.3 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 e-mail to the sponsor (Otsuka Global Intake: Global_Intake@otsuka-us.com). The sponsor is responsible for coordinating the reporting of SAEs/IREs in accordance with the European Directive 2001/20/EC.

Patient confidentiality must be protected and contact information such as name, address, telephone number, or any other protected health information as determined by applicable local regulation should be redacted when forwarding Safety Information and supporting documentation.

8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.8.5 Adverse Events of Special Interest

Not applicable.

8.8.6 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥3 x ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥2 x ULN, complete an IRE form with all values listed and also report as an AE on the eCRF.

8.8.7 Procedure for Breaking the Blind

This trial will not use blinding procedures.

8.8.8 Follow-up of Adverse Events

8.8.8.1 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 on the eCRF. For any AE having been identified throughout the trial, 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).

8.8.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 30 days after the 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 8.8.3.

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 IREs until the events are:

- resolved,
- stabilized,
- the subject is lost to follow-up, or
- 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 10.4 for additional information regarding the follow-up period for pregnant partners of male subjects.

8.8.8.3 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 IMP, should be reported to the sponsor according to the procedures outlined in Section 8.8.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.9 Treatment of Overdose

There is no specific antidote for OPC-61815 and its primary active metabolite, OPC-41061. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia, and these would be managed as medically appropriate (refer to the IB Section 6.3 for overdose treatment).[1]

8.10 Subject Assessment Recording

Not applicable.

8.11 Other Assessments

Not applicable.

9 Statistical Considerations

9.1 Sample Size

No formal statistical assessment of sample size has been conducted. The sample size chosen for this trial is common in human radiolabeled studies and is considered sufficient to achieve the objectives of the trial. It is planned for at least 8 healthy male Japanese subjects to be dosed to ensure that 6 subjects complete the IV infusion. Up to a maximum of 10 subjects will be dosed in total.

9.2 Datasets for Analysis

The safety population will include all subjects that received (^{14}C)-OPC-61815.

The PK population will include all subjects that received (^{14}C)-OPC-61815 (full dose within the time frame of 55 to 65 minutes, inclusive) and have evaluable PK data.

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analysis

Please refer to the Statistical Analysis Plan for these details.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analysis

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (latest version at time of data reporting) preferred term. The incidence of the following events will be summarized:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to withdrawal of IMP/withdrawal from study

9.4.2.2 Clinical Laboratory Data

Data will be summarized and listed by subject. No formal statistical analysis will be performed.

9.4.2.3 Physical Examination and Vital Signs Data

Vital sign data will be summarized and listed by subject. Physical examination data will be listed by subject. No formal statistical analysis will be performed.

9.4.2.4 Electrocardiogram Data

Data will be summarized and listed by subject. No formal statistical analysis will be performed.

9.4.2.5 Other Safety Data

Weight data will be summarized and listed by subject. No formal statistical analysis will be performed.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Data will be summarized and listed by subject. No formal statistical analysis will be performed.

9.4.3.2 Pharmacokinetic Analysis

For the primary objectives, the following PK parameter endpoints for OPC-61815 free form and OPC-41061 in plasma, and total radioactivity in whole blood and plasma will be calculated using standard noncompartmental methods: AUC from time zero to infinity (AUC_∞), AUC calculated to the last observable concentration at time t (AUC_t), C_{max}, time to maximum peak concentration (t_{max}), time of last measurable (positive) concentration (t_{last}), and terminal-phase elimination half-life ($t_{1/2,z}$). The total body clearance (CL) will also be determined for OPC-61815 free form. In addition, AUC ratios of whole blood total radioactivity relative to plasma total radioactivity (ratios of Blood/Plasma Ratio for both AUC_∞ and AUC_t) will be calculated. The following PK parameter endpoints for total radioactivity in urine will be calculated: amount excreted in urine ($Ae_{,u}$), cumulative $Ae_{,u}$, percentage excreted in urine ($\%fe_{,u}$), and cumulative $\%fe_{,u}$; and the following PK parameter endpoints for total radioactivity in feces will be calculated: amount excreted in feces ($Ae_{,f}$), cumulative $Ae_{,f}$, percentage excreted in feces ($\%fe_{,f}$), and cumulative $\%fe_{,f}$. Overall amount and percent of total radioactivity in excreta (combined urine and feces) will be calculated.

Additional noncompartmental PK parameters may be determined where appropriate.

Pharmacokinetic parameters will be summarized using descriptive methodology. No formal statistical analysis will be performed.

For the primary objective to identify and characterize metabolites in plasma, urine, and feces, the endpoint is the metabolic profile of (^{14}C)-OPC-61815 and identification of radiolabeled metabolites present at >10% of the total drug-related exposure (AUC) plasma.

9.4.3.3 Pharmacodynamics Analysis

No pharmacodynamics analysis is planned.

9.4.3.4 Pharmacokinetic/Pharmacodynamics Analysis

Not applicable.

9.4.3.5 Pharmacogenomics Analysis

No pharmacogenomics analysis is planned.

9.4.3.6 Exploratory Endpoint Analysis

Not applicable.

9.5 Interim Analysis and Adaptive Design

No interim analysis or adaptive design is applicable.

9.5.1 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, International Council for Harmonisation (ICH) GCP: Consolidated Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. The trial site will seek approval/favorable opinion by an EC according to regional requirements, and the investigator will provide that documentation to the sponsor. The EC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling eCRF and safety information, including IREs, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject 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 EC that approves this protocol.

Each ICF will comply with the ICH GCP: Consolidated Guideline E6[6] 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 EC.

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 the ICF by trial site staff. 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 EC-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 EC. 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 results 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 nonsubject partner and fetus.

10.1.3 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 IMPs, 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 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.

10.1.4 Quality Control and Quality Assurance

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH GCP: Consolidated Guideline (E6), 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.

10.1.4.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents,

the informed consent process, and a review of the eCRF with source documents, as applicable. The investigator agrees to 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.

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg,violation of informed consent process, IMP dispensing or subject dosing 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.

10.1.6 Records Management

10.1.6.1 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, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator/institution will permit trial-related monitoring, audits, EC 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.

10.1.6.2 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 process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- 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 IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- 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.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's electronic data capture (EDC) system that is 21 CRF Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

Electronic data not entered on eCRF, such as data received from central laboratories and central ECG readers, will be reconciled using key data fields by the sponsor or the Contract Research Organization with the eCRF data to ensure consistency.

10.1.6.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP: Consolidated Guideline (E6) and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.6.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

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 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 time frame. Notice of such transfer will be given to the sponsor in writing.

10.1.6.5 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 trial subjects 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 trial subjects consent to such acknowledgment in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Evaluations

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

Table 10.2-1 Clinical Laboratory Evaluations

Hematology: Hematocrit Hemoglobin (HGB) Ery. Mean Corpuscular HGB Ery. Mean Corpuscular HGB Concentration Ery. Mean Corpuscular Volume Platelet count Erythrocyte count Leukocytes count with differential Urinalysis: Occult Blood Glucose ketones Microscopic analysis, White Blood Cell/Red Blood Cell counts per high powered field pH Protein Specific Gravity	Serum Chemistry: Alkaline Phosphatase Alanine Aminotransferase Aspartate Aminotransferase Uric acid Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma Glutamyl Transferase Glucose Lactic Dehydrogenase Inorganic phosphate Potassium Total bilirubin Total protein Sodium Triglycerides
Serology (only analyzed at Screening) Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV): HIV-1 and HIV-2 antibodies and p24 antigen	Drug screen (only analyzed at Screening and Check-in) Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Cotinine Ecstasy Methadone Phencyclidine Opiates Oxycodone Tetrahydrocannabinol/cannabinoids Tricyclic antidepressants Alcohol breath test

10.3 Appendix 3: Total Blood Volume

The following blood volumes are the maximum that will be withdrawn for each subject.

Table 10.3-1 Total Blood Volume

		Up to Day 9 (inclusive)[a]	
	Volume per blood sample (mL)	**Maximum number of blood samples**	**Total amount of blood (mL)**
Clinical laboratory evaluations	7.5	6	45
Serology	3.5	1	3.5
Plasma for OPC-61815 free form and OPC-41061 concentrations	3	10	30
Whole blood for total radioactivity	2	16	32
Plasma for total radioactivity	5	16	80
Plasma for metabolite profiling and identification	10	15	150
Total			340.5

[a] Subjects could be discharged on Day 9 if the discharge criteria are met or may be resident within the Clinical Research Unit for an additional 24-hour collection (blood) for total radioactivity up to Day 10.

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Male subjects with partners of non-childbearing potential (defined as permanently sterile [due to hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy as reported by medical history and/or medical records; surgical sterilization to have occurred a minimum of 6 weeks, or at the investigator's discretion, prior to Screening] or postmenopausal [defined as females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason]) must use a male barrier method of contraception (ie, male condom with spermicide) from Check-in until 90 days after Final Discharge.

Male subjects (even with history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Check-in until 90 days after Final Discharge. Acceptable second methods of contraception for female partners include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant (as prescribed)
- hormonal or non-hormonal intrauterine device (as prescribed)
- over-the-counter sponge with spermicide
- diaphragm in conjunction with spermicide (as prescribed)
- cervical cap in conjunction with spermicide (as prescribed)

An acceptable second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success.

Sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of Check-in until 90 days after Final Discharge. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after Final Discharge.

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of trial participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Before enrolling males in this clinical trial, investigators must review the below 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 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.

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).

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 30 days after dose of IMP, 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.

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.

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Liver function tests should be promptly performed in subjects taking (^{14}C)-OPC-61815 who report symptoms that may indicate liver injury, including fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, jaundice, or dark urine. If liver injury is suspected, appropriate treatment should be instituted, and investigations should be performed to determine the probable cause.

10.6 Appendix 6: Abbreviations

Abbreviation	Definition
AE	Adverse event
$Ae_{,f}$	Amount excreted in feces
AESI	Adverse event of special interest
$Ae_{,u}$	Amount excreted in urine
ALARA	as low as (is) reasonably achievable
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
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
CL	Total body clearance
C_{max}	Maximum peak concentration of the drug
CRU	Clinical Research Unit
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
$\%fe_{,f}$	Percentage excreted in feces
$\%fe_{,u}$	Percentage excreted in urine
GCP	Good Clinical Practice
HGB	Hemoglobin
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICRP	International Commission in Radiological Protection
IMP	Investigational medicinal product
IRE	Immediately reportable event
IV	Intravenous
PHE	Public Health England
PK	Pharmacokinetic
PQC	Product quality complaint
SAE	Serious adverse event
$t_{1/2}$	Elimination half-life
$t_{1/2,z}$	Terminal-phase elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum peak concentration
ULN	Upper limit of normal

10.7 Appendix 7: 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 EC. Any permanent change to the protocol, whether an overall change or a change for specific trial site, must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the EC, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for EC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative 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 IMP 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 EC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the EC, 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 EC, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

10.7.1 Protocol Amendment(s)/Administrative Change(s)

10.7.1.1 Protocol Amendment 1

Amendment 1 Approval Date: 14 November 2019

PURPOSE:

- To increase the time window for clinical laboratory evaluations from ±60 minutes to ±120 minutes for the 24- and 48-hour postdose safety samples.
- To clarify that subjects may be dosed either in the morning or in the afternoon.

BACKGROUND:

The changes are needed for logistical reasons at the site.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- The trial design section was amended to remove the specification that subjects will be dosed, and associated additional excreta samples will be collected, in the morning.
- The time windows for clinical laboratory evaluations at the 24- and 48-hour timepoints relative to the start in infusion were updated to ±120 minutes.

ADDITIONAL RISK TO THE SUBJECT:

There are no additional risks to the subjects.

11 References

1. Otsuka Pharmaceutical Co., Ltd. OPC-61815 - Investigator's Brochure (Version 8). 2019.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2) Questions and Answers (R2) [Internet]. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2012. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf

3. ICRP. Radiological Protection in Biomedical Research. ICRP Publ 62 Ann ICRP. 1992;22(3).

4. Public Health England, London, UK. Assessment of the Radiation Dose to Male Volunteers from the Intravenous Dosing of 14C-OPC-61815. 2019.

5. World Health Organization. Use of ionising radiation and radionuclides on human beings for medical research, training, and nonmedical purposes. 1977.

6. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) [Internet]. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2016. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

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, (^{14}C)-OPC-61815, 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 or receive a favorable opinion by the Independent Ethics Committee responsible for such matters in the clinical trial facility where (^{14}C)-OPC-61815 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 EC-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 EC 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 EC within the required local applicable timelines Administrative changes to the protocol will be transmitted to the EC 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.

PPD [redacted]

Principal Investigator Print Name Signature Date

PPD [redacted]

Sponsor Representative Print Name Signature Date