CLINICAL STUDY PROTOCOL

A Single-center, Randomized, Double-blind (for OPC-61815 and Placebo), Placebo- and Moxifloxacin Positive-controlled, 4-Period Crossover Trial to Evaluate the Effect of Single Intravenous Administration of OPC-61815 at 16 and 32 mg on QT/QTc Interval in Healthy Male Subjects

NCT Number: NCT03510663
PRT NO.: 263-102-00005
Version Date: 27 February 2018 (Version 1.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

OPC-61815

CLINICAL PROTOCOL

A Single-center, Randomized, Double-blind (for OPC-61815 and Placebo), Placebo- and Moxifloxacin Positive-controlled, 4-Period Crossover Trial to Evaluate the Effect of Single Intravenous Administration of OPC-61815 at 16 and 32 mg on QT/QTc Interval in Healthy Male Subjects

Protocol No. 263-102-00005

CONFIDENTIAL - PROPRIETARY INFORMATION

Clinical Development Phase: 1

Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event:	Department of Pharmacovigilance Otsuka Pharmaceutical Co., Ltd. Email: IRE_263-102-00005@otsuka.jp
Issue Date:	27 Feb 2018
Protocol Version Number:	1.0
Date of Translation:	10 Sep 2018

Protocol Synopsis

<table>
<tr><td colspan="2">Name of Sponsor: Otsuka Pharmaceutical Co., Ltd.
Name of Investigational Medicinal Product:
OPC-61815</td><td>Protocol No.: 263-102-00005</td></tr>
<tr><td>Protocol Title:</td><td colspan="2">A Single-center, Randomized, Double-blind (for OPC-61815 and Placebo), Placebo- and Moxifloxacin Positive-controlled, 4-Period Crossover Trial to Evaluate the Effect of Single Intravenous Administration of OPC-61815 at 16 and 32 mg on QT/QTc Interval in Healthy Male Subjects</td></tr>
<tr><td>Clinical Phase:</td><td colspan="2">Phase 1</td></tr>
<tr><td>Treatment Indication:</td><td colspan="2">Congestive heart failure (CHF) patients with volume overload despite having received diuretics other than vasopressin antagonists</td></tr>
<tr><td>Objective(s):</td><td colspan="2">To investigate the effects of 1-hour intravenous administration of OPC-61815 at 16 and 32 mg on QT/QTc interval in healthy male subjects</td></tr>
<tr><td>Trial Design:</td><td colspan="2">Single-center, randomized, double-blind, placebo- and moxifloxacin positive-controlled, 4-period crossover trial
<table><tr><td>Period 1</td><td>Period 2</td><td>Period 3</td><td>Period 4</td></tr><tr><td colspan="4">Single administration of OPC-61815 at 16 or 32 mg, placebo, or moxifloxacin at 400 mg</td></tr><tr><td colspan="4">In each treatment period, subjects will be admitted on the day before administration of investigational medicinal product (IMP) and discharged on Day 2.</td></tr></table>A washout period of ≥6 days will be set from the day after IMP administration in each period until the start of administration in the next treatment period.</td></tr>
<tr><td>Subject Population:</td><td colspan="2">Total of 48 healthy male subjects age 20 to 45 years, inclusive</td></tr>
<tr><td>Inclusion/Exclusion Criteria:</td><td colspan="2">Inclusion Criteria:
1) Japanese male subjects age 20 to 45 years, inclusive, at time of informed consent
2) Body mass index (BMI) (body weight in kg / [height in m]^2) of at least 18.5 kg/m^2 and less than 25.0 kg/m^2 as a result of at the screening examination
3) Judged by the investigator or subinvestigator to be capable of providing written informed consent prior to start of any trial-related procedures and capable of complying with the procedures for this trial
Exclusion Criteria:
1) Subjects with a medical history of convulsive disorder,</td></tr>
</table>

long QT syndrome (including family history), syncope during swimming, or any other type of syncope or cryptogenic loss of consciousness

2) Subjects with a serum electrolyte abnormality (hypokalemia, hypomagnesemia, hypocalcemia, etc)
3) Subjects with a family history of sudden death
4) Subjects with a history of heart disease such as hypertension, atherosclerosis, heart failure, bradycardia, or stroke, or who are using a pacemaker
5) Subjects with 2 or more of the following abnormalities in 3 tests of 12-lead electrocardiography (ECG) and 2 or more additional abnormalities in re-testing performed 1 hour after the first series of tests at the screening examination or on the day before Period 1 IMP administration (Day −1)

- PR interval of >220 msec
- QRS interval of >120 msec
- QTcF of <320 msec or >450 msec
- Atrial fibrillation or atrial flutter
- Other worrisome cardiac findings

6) Subjects who have received any other IMP in another clinical trial within 120 days prior to Period 1 IMP administration
7) Subjects who have undergone blood collection (eg, blood donation) of >200 mL within 30 days, >400 mL within 90 days, or >1200 mL within 1 year prior to Period 1 IMP administration
8) Subjects who have consumed any of the following products within the corresponding specified time prior to Period 1 IMP administration

- Products containing St John's wort (Hypericum perforatum): Within 14 days prior to Period 1 IMP administration
- Grapefruit, Seville orange, or star fruit, or products processed from any of them: Within 7 days prior to Period 1 IMP administration
- Food or beverages containing alcohol or caffeine: Within 1 day prior to Period 1 IMP administration

9) Subjects who have taken any prescription drugs, OTC drugs, Chinese herbal remedies, or vitamin supplements within 14 days or antibiotics within 30 days prior to Period 1 IMP administration
10) Subjects who have been exposed to any substance known to stimulate production of liver microsomal

enzymes (eg, occupational exposure to pesticides or organic solvents) within 30 days prior to Period 1 IMP administration

11) Subjects who have used any tobacco products, nicotine replacement therapy, or electronic cigarettes or who have been exposed to second-hand smoke on a daily basis, within 60 days prior to Period 1 IMP administration, or who test positive in urine nicotine test at the screening examination

12) Subjects who are sexually active but unable or unwilling to either use 2 types of approved contraception methods or remain abstinent during the trial and for 30 days after final IMP administration, or who plan to donate sperm during the period from the screening visit until 30 days after final IMP administration

13) Subjects with a history of a clinically significant abnormality, or for whom a clinically significant abnormality is observed in the results of the screening examination, and the investigator, subinvestigator, or sponsor judges that the abnormality could place the subject at risk or affect evaluation of drug absorption, distribution, metabolism, or excretion

    Such abnormalities include, but are not limited to, a history or current symptoms of cardiac, hepatic, renal, nervous system, endocrine, gastrointestinal, respiratory, hematologic, and immune diseases/disorders.

14) Subjects with a history of clinically significant drug or alcohol abuse

15) Subjects with a history or current condition of hepatitis or acquired immunodeficiency syndrome (AIDS), or a positive test result for any of the following: Hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibody, AIDS antigen/antibody, or syphilis

16) Subjects with a history of severe drug allergy or hypersensitivity to any of the following drugs:

- Any ingredients of OPC-61815 or tolvaptan
- Compounds containing benzazepine (mozavaptan hydrochloride, benazepril hydrochloride)
- Quinolone antibiotics, including moxifloxacin

17) Subjects who have a positive test result in breath

	alcohol test or urine drug test for detection of substance abuse at the screening examination or on the day before Period 1 IMP administration (Day −1) 18) Subjects with a history of serious hemorrhage or bleeding tendency 19) Subjects with blood collection difficulty 20) Subjects with supine resting systolic blood pressure of >140 mmHg or <90 mmHg or supine resting diastolic blood pressure of >80 mmHg or <40 mmHg at the screening examination or on the day before Period 1 IMP administration (Day −1) 21) Subjects with supine resting pulse rate of >90 bpm or <45 bpm at the screening examination or on the day before Period 1 IMP administration (Day −1) 22) Subjects who are currently taking an antiarrhythmic agent of Class IA (quinidine, procainamide, etc) or Class III (amiodarone, sotalol, etc) 23) Subjects with a history of serious psychological disorder whose participation in the clinical trial is judged to be inappropriate by the investigator or subinvestigator 24) Subjects who are otherwise judged by the investigator or subinvestigator to be inappropriate for participation in the clinical trial
Trial Site(s):	Soseikai Fukuoka Mirai Hospital Clinical Research Center
Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:	OPC-61815 at 16 or 32 mg will be intravenously administered once by 1-hour infusion on the first day of each treatment period.
Reference Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:	Placebo injection corresponding to the dose of OPC-61815 will be intravenously administered once by 1-hour infusion on the first day of each treatment period. One moxifloxacin 400 mg tablet will be orally administered once on the first day of each treatment period.
Trial Assessments:	Pharmacokinetics: Blood collection for measurement of plasma drug concentrations Pharmacodynamics: 12-Lead Holter ECG

	Safety: Adverse event reporting, clinical laboratory assessments, physical examination, vital signs, body weight, and 12-lead ECG Screening/other: Medical and medication history, breath alcohol test, urine drug screening, and blood screening for infectious diseases
Criteria for Evaluation:	**Primary Endpoint**: Time-matched difference between the OPC-61815 and placebo data in change from baseline for QTcF in 12-lead Holter ECG **Secondary Endpoints:** 12-Lead Holter ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval) and ECG waveform patterns **Pharmacokinetic Endpoints:** Plasma concentrations and pharmacokinetic parameters of OPC-61815 free form and tolvaptan **Safety Endpoints:** Adverse event reporting, clinical laboratory assessments, physical examination, vital signs (blood pressure, pulse rate, and body temperature), body weight, and 12-lead ECG
Statistical Methods:	**Statistical Methods for Primary Endpoint:** Central tendency analysis for OPC-61815 will be performed for subjects in the pharmacodynamic analysis set who completed all IMP treatments and for whom predose and postdose QT data are available for all 4 treatment periods. For each OPC-61815 dose, the upper limit of the 2-sided 90% confidence interval (CI) for the time-matched difference in the least squares mean for the change in QTcF from baseline compared to the placebo data will be evaluated to determine if it is lower than 10 msec at all postdose time points. Using a linear mixed effect model with baseline QTcF in each treatment period as a covariate, treatment, sequence, treatment period, time point, and interaction between treatment and time point as fixed effects, and subject as a random effect, point estimates and 2-sided 90% CIs for the time-matched

	difference in the least squares mean for the change in QTcF from baseline compared to the placebo data will be calculated. **Rationale for Determination of Sample Size** The number of subjects required for central tendency analysis of QTcF, the primary endpoint, was calculated. The number of subjects was calculated to achieve a ≥90% probability of the upper limit of the 2-sided 90% CI (1-sided 95% CI) for the time-matched difference in the mean values for the change in QTcF from baseline between the OPC-61815 and placebo values being lower than 10 msec at all time points after administration of each OPC-61815 dose (16 and 32 mg), and a ≥90% probability of the lower limit of the 2-sided 98% CI (1-sided 99% CI) for the time-matched difference in the mean values for the change in QTcF from baseline between the moxifloxacin and placebo values being higher than 0 msec in at least one of the 5 assay sensitivity assessment time points (1, 1.5, 2, 3, and 4 hours) after administration of the positive control moxifloxacin. For the assay sensitivity CI, the increase of type 1 error due to the multiplicity of multiple time points was corrected using the Bonferroni method. Assuming the within-subject standard deviation to be 7.86, the effect size of moxifloxacin to be 9.6 msec based on the results of a previous trial (Protocol 331-10-242, a clinical trial of brexpiprazole for evaluation of QT/QTc interval in patients with schizophrenia and schizoaffective disorder), the effect size of OPC-61815 to be 3.0 msec (although no data are available) and the individual time points to be independent, the required number of subjects is 45 for each OPC-61815 dose and 21 for moxifloxacin. Estimating a 5% discontinuation rate, a sample size of 48 subjects was considered necessary.
Trial Duration:	Total duration of the trial: Apr to Jul 2018 (The total duration of the trial for each subject will be a

	maximum of 58 days, assuming a 6-day washout period between each treatment period, comprising the following trial periods:) • Screening: Day −28 to Day −2 • Periods 1 through 3: ≥7 days for each treatment period (1 day for administration and ≥6 days for washout) • Period 4: 2 days • Post treatment follow-up period: 6 to 8 days after the last IMP administration in Period 4

Table of Contents

List of In-text Tables

List of In-text Figures

List of Appendices

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AVP	Arginine vasopressin
BMI	Body mass index
cAMP	Cyclic adenosine 3', 5'-monophosphate
CK (CPK)	Creatine kinase
CYP	Cytochrome P450
ECG	Electrocardiography
GCP	Good Clinical Practice
γ-GTP	γ-glutamyltransferase
HBsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
hERG	Human ether-a-go-go related gene
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional review board
IRE	Immediately reportable event
LDH	Lactic dehydrogenase
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean Corpuscular Volume
PQC	Product quality complaint
PK	Pharmacokinetics
QT	QT interval
QTc	QT corrected for heart rate
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
TEAE	Treatment-emergent adverse event

List of Pharmacokinetic Parameters

Abbreviation/ Term	Unit	Spelled-out Form or Definition
AUC_{∞}	ng·h/mL	Area under the concentration-time curve from time zero to infinity
AUC_{24h}	ng·h/mL	Area under the concentration-time curve from time zero to 24 hours
AUC_t	ng·h/mL	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC_%Extrap	%	Percentage of AUC due to extrapolation from t_{last} to infinity [$(AUC_{\infty} - AUC_t)/AUC_{\infty} \times 100$]
CL	L/h	Total body clearance of drug from the plasma
CL/BW	L/h/kg	CL normalized in body weight
C_{max}	ng/mL	Maximum (peak) plasma concentration of the drug
λ_z	h^{-1}	Apparent terminal-phase disposition rate constant (first-order)
λ_z(point)		Number of points used in computing λ_z. If λ_z cannot be estimated, zero
λ_z(lower)	h	Lower limit on Time for values to be included in the calculation of λ_z
λ_z(upper)	h	Upper limit on Time for values to be included in the calculation of λ_z
λ_z(Rsq)		Goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z
$t_{1/2,z}$	h	Terminal-phase elimination half-life
t_{last}	h	Time of last measurable (positive) concentration
t_{max}	h	Time to maximum (peak) plasma concentration
V_z	L	Apparent volume of distribution during the terminal (λ_z) phase

1 Introduction

Tolvaptan is an orally effective nonpeptide arginine vasopressin (AVP) V_2 receptor antagonist synthesized by Otsuka Pharmaceutical Co., Ltd. (hereinafter referred to as Otsuka) that inhibits water reabsorption in renal collecting ducts, thereby inducing an increase in water diuresis (aquaresis) without affecting electrolyte excretion.

In Japan, tolvaptan was approved in 2010 under the trade name of Samsca tablets® 15 mg for the indication of "volume overload in heart failure when an adequate response is not obtained with other diuretics (eg, loop diuretics)." In 2013, a new indication of "body fluid retention in hepatic cirrhosis when an adequate response is not obtained with other diuretics (eg, loop diuretics)" was approved. In 2014, an additional marketing approval for the suppression of progression of autosomal dominant kidney disease (ADPKD) in patients with increased kidney volume and a rapid rate of increase was granted. The additional marketing approvals were granted for Samsca 7.5 mg tablet in 2013 and 30 mg tablet in 2014. Outside Japan, tolvaptan was approved for the treatment of clinically significant hypervolemic and euvolemic hyponatremia including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in the US and for the treatment of hyponatremia secondary to SIADH in adult patients in Europe in 2009. In 2015, an additional marketing approval for indication to slow the progression of cyst development and renal insufficiency of ADPKD in adults with chronic kidney disease (CKD) Stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease was granted in Europe. Tolvaptan has been approved in over 40 countries/regions.

Tolvaptan has been developed only as oral tablets because clinical development of tolvaptan in injection formulation has been difficult due to the low water solubility. Used as an oral aquaretic, tolvaptan provides a useful treatment option in clinical practice for the above-approved indications. However, there are unmet medical needs for intravenous aquaretics with a similar effect to oral tolvaptan for patients with impaired consciousness who are unable to take oral drugs, patients who cannot adequately absorb oral drugs due to gastrointestinal edema, patients on continuous oxygen therapy who therefore have difficulty taking oral drugs, and elderly patients with decreased swallowing function. Under such circumstances, Otsuka synthesized a new intravenous aquaretic, OPC-61815. OPC-61815 is a compound with improved water solubility achieved by phosphorylation of the hydroxyl group in the benzazepine ring of tolvaptan. When administered, the phosphate ester of OPC-61815 is hydrolyzed by alkali and acid phosphatase in the body to form tolvaptan as an active substance of OPC-61815, which is considered to work as

an aquaretic. OPC-61815 is under development with the expectation that it will have a beneficial therapeutic effect.

So far, the following three phase 1 trials of OPC-61815 have been completed in healthy adult male subjects: single intravenous dose trial (263-08-001), repeated intravenous dose trial (263-09-001), and trial investigating the rate of intravenous administration (263-10-005). Based on the results of these trials, another trial is currently ongoing to investigate the dose of OPC-61815 intravenous injection that achieves an exposure equivalent to that obtained with tolvaptan 15-mg oral tablet in patients with congestive heart failure.

Tolvaptan, the active substance of OPC-61815, and its metabolites demonstrated no QTc interval prolongation in a completed trial (156-03-245) evaluating the effects of oral tolvaptan on the QTc interval in healthy subjects. However, the effect of OPC-61815 on the QTc interval before being metabolized into tolvaptan has yet to be studied. Otsuka has therefore decided to conduct this trial in healthy adult volunteers to evaluate the effect of OPC-61815 on the QT/QTc interval.

Please refer to the Investigator's Brochure (IB) for further information on the results of nonclinical studies and clinical trials of OPC-61815. [1] Nonclinical and clinical data are summarized below.

1.1 Nonclinical Data

1.1.1 Efficacy Pharmacology

In a receptor-binding study using [^{3}H]-AVP as a labeled ligand, OPC-61815 exhibited affinity for the human AVP V_2 receptor (K_i value: 6.13 ± 1.34 nM), but that affinity was about 1/14 that of the primary active metabolite tolvaptan (K_i value: 0.43 ± 0.06 nM). OPC-61815 also showed weak affinity for the human AVP V_{1a} receptor (K_i value: 54.2 ± 16.8 nM), only 1/4 that of tolvaptan (K_i value: 12.3 ± 0.80 nM). Like tolvaptan, OPC-61815 did not show affinity for the human AVP V_{1b} receptor. OPC-61815 and tolvaptan showed an antagonistic action against the V_2 receptor in HeLa cells expressing the human AVP V_2 receptor by inhibiting the production of cyclic adenosine 3',5'-monophosphate (cAMP) by AVP. However, neither OPC-61815 nor tolvaptan induced any increase in cAMP production by itself, indicating that they possess no intrinsic V_2 receptor agonistic activity.

Conscious rats given a single intravenous administration of OPC-61815 (0.1275 to 12.75 mg/kg) showed a dose-dependent increase in urine volume and decrease in urine

osmolality. These changes were not attenuated with 7-day repeated intravenous dosing. Beagle dogs given single intravenous administration of OPC-61815 (0.1275 to 3.825 mg/kg) showed a dose-dependent increase in urine volume and decrease in urine osmolality. Free water clearance was dose-dependently increased in these dogs, indicating that OPC-61815 is an aquaretic agent which increases free water excretion. Dogs given a single intravenous administration of OPC-61815 showed an increase in plasma AVP concentrations without increase in plasma renin activity. This showed that, unlike furosemide, OPC-61815 does not activate the renin-angiotensin system.

In a rat model of hyponatremia receiving 5 days of dose-escalating intravenous administration of OPC-61815 (0.255 to 5.1 mg/kg) showed an increase in the lowered plasma sodium concentration as the dose was increased. Water content in the brain and heart was increased due to hyponatremia, but it was improved after OPC-61815 administration.

Histamine-induced vascular hyperpermeability model rats showed a dose-dependent increase in urine volume and decrease in urine osmolality after a single intravenous administration of OPC-61815 (0.3825 to 3.825 mg/kg, 2 hours before histamine dosing), with a dose-dependent reduction in the area of pigment leakage at the histamine administration site. In a carrageenan-induced paw edema model, development of paw edema was dose-dependently inhibited after a single intravenous administration of OPC-61815 (1.275 to 12.75 mg/kg, 1 hour before carrageenan dosing).

These study results demonstrated the potent water diuretic action of intravenous OPC-61815 as also observed with tolvaptan, thus showing its promising clinical efficacy in the treatment of various conditions associated with volume overload due to abnormal water metabolism such as hyponatremia and edematous disorders.

1.1.2 Safety Pharmacology/General Pharmacology

The effects of OPC-61815 on the central nervous system (CNS) (general conditions and behavior), respiratory and cardiovascular systems, and human ether-a-go-go related gene (hERG) current were evaluated.

A single dose of OPC-61815 was intravenously administered to male Sprague-Dawley rats at 0 (vehicle control), 12.75, 63.75, and 255 mg/kg to evaluate its effect on the CNS (general conditions and behavior). Doses of 12.75 mg/kg and higher increased urine output, and a dose of 255 mg/kg decreased spontaneous motor activity, contact reaction, body tension, and respiratory rate and was associated with abnormal posture.

A single dose of OPC-61815 was intravenously administered to unanesthetized male beagle dogs at 0 (vehicle control), 12.75, 38.25, and 127.5 mg/kg to evaluate its effect on the respiratory and cardiovascular systems. Doses of 12.75 mg/kg and higher increased urine output and concentration of plasma sodium and chloride and decreased the T wave amplitude. Doses of 38.25 mg/kg and higher increased heart rate. A dose of 127.5 mg/kg caused vomiting, increased respiratory rate, and decreased blood pressure and PR interval. Histamine release-related vasodilatation was considered to be involved in a fall in blood pressure, and experiments were conducted in anesthetized male beagle dogs. OPC-61815 decreased blood pressure, increased heart rate, and slightly elevated plasma histamine concentrations immediately after a single intravenous administration at 100 mg/kg. However, pretreatment with an antihistamine did not prevent a drop in blood pressure. Based on these findings, it was concluded that the observed reduction in blood pressure was unrelated to the elevation in endogenous histamine levels.

The effect of OPC-61815 on hERG current was evaluated in Chinese hamster ovary cell-derived cell line (CHO-K1 cells) at concentrations of 0 (vehicle control), 10^{-6}, 10^{-5}, and 10^{-4} mol/L. OPC-61815 had no effect on hERG current.

1.2 Clinical Data

1.2.1 Single Intravenous Dose Trial in Healthy Adult Males (Phase 1) (Protocol No. 263-08-001)

In the phase 1 single intravenous dose trial (263-08-001), 54 healthy adult male subjects were given an intravenous administration (by 5-minute infusion) of OPC-61815 at 0.3, 1, 3, 7.5, 15, or 30 mg or placebo. The plasma concentration of OPC-61815 free form reached a peak between the completion of injection and 0.020 hours after injection (median of time to maximum [peak] plasma concentration [t_{max}]) and quickly decreased to below the lower limit of quantitation (46.2 ng/mL) by 8 hours postdose in every dose group. The peak plasma concentration (C_{max}), area under the concentration-time curve from time zero to infinity (AUC_{∞}), and area under the concentration-time curve calculated to the last observable concentration at time t (AUC_t) increased as the dose was increased. The mean terminal-phase elimination half-life ($t_{1/2,z}$) was 0.63 to 1.7 hours. Tolvaptan rapidly appeared in the plasma following intravenous administration of OPC-61815, with the plasma concentration peaking between 0.5 and 1.0 hours postdose and then decreasing to below the lower limit of quantitation (2.00 ng/mL) by 72 hours postdose in every dose group. The C_{max}, AUC_{∞}, and AUC_t all increased dose-

dependently, and the mean $t_{1/2,z}$ was between 2.2 and 5.7 hours. A dose-dependent increase in urine volume was observed following a single intravenous administration of OPC-61815 at 3 to 30 mg. There was little change in urine electrolyte excretion. Serum sodium concentration and serum osmolality increased, but there were no changes in serum potassium concentration. In terms of safety, all adverse events (AEs) reported in subjects treated with OPC-61815 were mild and resolved without treatment or with palliative treatment.

1.2.2 Repeated Intravenous Dose Trial in Healthy Adult Males (Phase 1) (Protocol No. 263-09-001)

In the phase 1 repeated intravenous dose trial (263-09-001), 36 healthy adult male subjects were given a single intravenous administration of OPC-61815 at 1.25, 5, or 20 mg or placebo, followed by a 1-day washout and repeated intravenous doses (by 1-minute infusion) for 7 days. No accumulation of OPC-61815 free form or its main active metabolite (tolvaptan) was seen. The AUC and C_{max} of plasma OPC-61815 free form and tolvaptan increased dose-dependently. During once-daily 7-day repeated intravenous administration of OPC-61815 at 5 and 20 mg, an increase in urine volume was observed. However, the increase did not expand in response to the 7-day repeated administration. In terms of safety, AEs that included feeling abnormal, pruritus, and erythema were reported frequently during and immediately after administration of OPC-61815. All the AEs were mild or moderate and subsequently resolved without treatment. However, because many of these events were judged to be potentially causally related to the investigational medicinal product (IMP) and were not reported in subjects treated with oral tolvaptan, it is suspected that OPC-61815 could be related to the occurrence of these events.

1.2.3 Intravenous Dose Trial on Rate of Injection in Healthy Adult Males (Phase 1) (Protocol No. 263-10-005)

This trial was conducted to investigate the method of administration that can avert the potentially drug-related AEs reported in the phase 1 repeated intravenous dose trial of OPC-61815 (263-09-001) and not reported in subjects treated with oral tolvaptan. The trial was also aimed at exploring the cause of these potentially drug-related AEs. Eighteen healthy adult male subjects were given a single intravenous administration of OPC-61815 at 7.5 or 15 mg or placebo over different durations (2 hours, 5 minutes, and 1 minute). The median t_{max} and mean $t_{1/2,z}$ of OPC-61815 free form after a 2-hour single intravenous administration were 1.8 to 2.0 hours and 1.0 to 1.3 hours, respectively. The mean C_{max} of OPC-61815 free form after 2-hour administration was approximately 70%

lower than that after 5-minute and 1-minute administration. The median t_{max} and mean $t_{1/2,z}$ of tolvaptan after 2-hour administration were 2.3 hours and 3.9 to 4.6 hours, respectively. The mean C_{max} of tolvaptan after 2-hour administration was comparable to that after 5- and 1-minute administration. The rate of increase in mean urine volume until 4 hours after a 2-hour single intravenous administration of OPC-61815 was lower than that after both 5- and 1-minute administrations. Postdose hyposthenuria associated with decreased mean urine osmolality was observed with a slight elevation in the mean serum osmolality and serum sodium concentrations. AEs similar to feeling abnormal, pruritus, and erythema, etc. that were frequently reported in the repeated intravenous dose trial of OPC-61815 (263-09-001) were selected as notable AEs (hereafter, AEs of special interest). These AEs of special interest occurred in 1 of 12 subjects (8.3%) in the OPC-61815 groups and in 3 of 6 subjects (50%) in the placebo group after 2-hour administration. An AE (rash) occurring in 1 OPC-61815-treated subject and AEs (feeling abnormal and urticaria) in 2 placebo-treated subjects were considered unrelated to IMP. AEs of special interest occurred in 9 of 12 subjects (75%) in the OPC-61815 groups and 2 of 6 subjects (33.3%) in the placebo group after 5-minute administration. All the events were judged to be related to IMP. The AEs of special interest were reported in 10 of 11 subjects (90.9%) in the OPC-61815 groups and in 4 of 6 subjects (66.6%) in the placebo group after 1-minute administration. All the events excluding an event of erythema in the OPC-61815 group were judged to be related to IMP. All the AEs causally related to IMP occurred during or immediately after intravenous administration. Most of those events resolved without treatment within 10 minutes after start of IMP administration. No severe cases were found among the AEs of special interest. Because there were no clinically significant changes from baseline in plasma histamine concentrations, the cause of the AEs of special interest is unclear.

1.2.4 Clinical Pharmacological Dose Investigation Trial in Patients with Congestive Heart Failure (Protocol No. 263-102-00001)

Based on the results of 3 phase 1 trials in healthy adult males (263-08-001, 263-09-001, and 263-10-005), a phase 2 clinical pharmacological trial is ongoing to investigate the dose of OPC-61815 that achieves exposure equivalent to that obtained with tolvaptan 15-mg tablet in patients with congestive heart failure with volume overload despite having received conventional diuretics other than vasopressin receptor antagonists.

1.3 Pharmacokinetics/Pharmacodynamics

As a reference, the results of a clinical thorough QT (tQT) trial of tolvaptan are summarized below.

1.3.1 Trial to Evaluate the Effect of Oral Tolvaptan on QTc in Healthy Adults (Protocol No. 156-03-245)

A trial was conducted in the United Sates to evaluate the effect of oral tolvaptan on the QTc interval (QTcI) in healthy adult males and females.[2] This was a parallel-group comparative trial to determine the mean change from baseline (mean) in QTcI at Day 1 following a single oral administration or at Day 5 following once-daily repeated oral administration. A total of 160 healthy adult male and female subjects were randomized to receive 400 mg moxifloxacin tablets, placebo, 30 mg tolvaptan, or 300 mg tolvaptan so that each treatment group included 40 subjects (20 men and 20 women).

The mean change in QTcI following single and repeated administrations in each tolvaptan group did not show a statistically significant prolongation of QTcI compared to the placebo group. On the other hand, the mean change in QTcI following single and repeated administrations in the 400 mg moxifloxacin group showed a statistically significant prolongation of QTcI compared to the placebo group. These findings indicated that neither tolvaptan nor its metabolites prolong QTcI.

In terms of safety, AEs occurred in 19 of 43 subjects (44.2%) in the 30 mg tolvaptan group, 33 of 43 subjects (76.7%) in the 300 mg tolvaptan group, 10 of 43 subjects (23.3%) in the placebo group, and 21 of 42 subjects (50.0%) in the moxifloxacin group. Frequently reported AEs (incidence ≥5% in each dose group) in tolvaptan-treated subjects included thirst, pollakiuria, dry mouth, abdominal pain, nausea, headache, and throat irritation. Frequently reported AEs in moxifloxacin-treated subjects included dizziness, abdominal pain, nausea, dry mouth, pollakiuria, and dermatitis contact. Frequently reported AEs in placebo-treated subjects included headache, nausea, and pollakiuria. All AEs were mild or moderate in severity, demonstrating favorable tolerability after repeated oral administration of 30 mg and 300 mg tolvaptan.

1.4 Risks and Benefits

No deaths or other serious adverse events (SAEs) were reported in the phase 1 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 the significant AEs reported following

intravenous administration of OPC-61815 in Trials 263-09-001 and 263-10-005. Feeling abnormal, feeling hot, erythema, hyperhidrosis, pruritus, rash, urticaria, nausea, epigastric discomfort, and dyspnea, all of which frequently occurred in Trial 263-09-001, were selected as AEs of special interest. In Trial 263-10-005, 1- and 5-minute administrations were associated with frequent occurrences of AEs of special interest in OPC-61815-treated subjects, whereas following a 2-hour administration, only 1 subject experienced an AE of special interest, and this was considered unrelated to IMP. These findings suggest that a longer duration of OPC-61815 administration would reduce the risk of developing these events. However, AEs of special interest reported in completed phase 1 trials occurred during or immediately after IMP administration. Although most events spontaneously resolved within 10 minutes after start of IMP administration, subjects should be closely monitored for skin symptoms following start of IMP administration.

This trial will use moxifloxacin 400-mg tablets as a positive control. Moxifloxacin has been approved in Japan as an oral quinolone antibiotic under the trade name of Avelox® tablets 400 mg. The incidence of potentially drug-related AEs (including abnormal laboratory changes) was 25.7% (130/505) in Japanese clinical trials of moxifloxacin 400-mg tablets conducted before the time of approval. Common potentially drug-related AEs included diarrhoea (24/505, 4.8%), liver function test abnormal (22/505, 4.4%), nausea (18/505, 3.6%), dyspepsia (14/505, 2.8%), and abdominal pain (12/505, 2.4%). The incidence of potentially drug-related AEs in non-Japanese clinical trials was 25.1% (2314/9225). Common potentially drug-related AEs included nausea (653/9225, 7.1%), diarrhoea (461/9225, 5.0%), and dizziness (233/9225, 2.5%). Since moxifloxacin may cause shock or anaphylaxis, subjects should be carefully interviewed to ascertain if there is a history of allergy and drug hypersensitivity prior to IMP administration.

This trial will enroll healthy adult males and subjects will receive no health benefit for their participation.

Please refer to the package insert of Avelox® tablets 400 mg[3] for further information on moxifloxacin.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Samsca tablets® (tolvaptan tablets) developed by Otsuka, used as an oral aquaretic agent in clinical practice, provide a useful treatment option in Japan for volume overload in heart failure when an adequate response is not obtained with other diuretics (eg, loop

diuretics). Under the circumstances where tolvaptan's poor water solubility has made it difficult to develop injectable formulations from tolvaptan, Otsuka synthesized the new intravenous aquaretic, OPC-61815. OPC-61815 is a compound with improved water solubility achieved by phosphorylation of the hydroxyl group in the benzazepine ring of tolvaptan. It is mandatory for OPC-61815, a novel compound, to be studied for its effect on the QT/QTc interval as specified in the International Council for Harmonization (ICH) Guideline E14.[4]

In relation to tolvaptan, a pharmacologically active substance, the effect of oral tolvaptan on the QTc interval was evaluated in a clinical trial in healthy adults (156-03-245). Tolvaptan or its metabolites did not prolong the QTc interval. However, the effect of OPC-61815 on QTc interval before being metabolized into tolvaptan has yet to be studied.

Otsuka has therefore decided to conduct this trial in healthy adult volunteers to evaluate the effect of OPC-61815 on the QT/QTc interval. This trial will use moxifloxacin as a positive control to ensure assay sensitivity.

Three phase 1 clinical trials of OPC-61815 in healthy adult male subjects have been completed and the safety of the compound has been confirmed. Moxifloxacin is an approved medicinal product.

In conclusion, the conduct of this trial is scientifically and ethically justified.

2.2 Dosing Rationale

2.2.1 Regimen

In a repeated dose trial (263-09-001) in which OPC-61815 was intravenously administered by 1-minute infusion, subjects experienced feeling abnormal (8/27, 29.6%), pruritus (4/27, 14.8%), pruritus generalized (3/27, 11.1%), and erythema (3/27, 11.1%), none of which occurred in a single dose trial (263-08-001) in which OPC-61815 was intravenously administered by 5-minute infusion. Prompted by these findings, an intravenous dose trial on rate of injection (263-10-005) was conducted to investigate if any relationship existed between the occurrence of potentially drug-related AEs and the rate of administration (2 hours, 5 minutes, and 1 minute). In this trial, 7.5 and 15 mg OPC-61815 was administered at different administration rates. As a result, the above potentially drug-related AEs occurred following 1- or 5-minute intravenous administration, whereas they did not occur following 2-hour intravenous administration.

These findings suggest that a longer duration of OPC-61815 administration would reduce the risk of developing the above potentially drug-related AEs.

PK models of plasma OPC-61815 and tolvaptan concentration were created using data from the prior phase 1 studies (263-08-001, 263-09-001, and 263-10-005) to perform simulations designed to investigate how the PK parameters of OPC-61815 and tolvaptan change in response to changes in rate of administration. The t_{max} of tolvaptan following simulated 2-hour intravenous administration of OPC-61815 was 2.25 hours, suggestive of longer t_{max} than that following actual oral administration of tolvaptan (2 hours). The t_{max} of tolvaptan following simulated 1-hour intravenous administration of OPC-61815 was 1.5 hours, a shorter t_{max} than that following actual oral administration of tolvaptan (2 hours), indicating that an earlier onset of action can be expected following 1-hour intravenous administration. Based on these simulation results, OPC-61815 will be intravenously administered by 1-hour infusion in this trial.

2.2.2 Dose

The ICH Guideline E14 states that the drug should be tested for QT/QTc prolongation at substantial multiples of the anticipated maximum therapeutic exposure, or that, if interactions involving metabolizing enzymes or transporters are expected, these effects could be studied under conditions of maximum inhibition.

The recommended clinical dose of OPC-61815 is planned to be 8 mg for patients with congestive heart failure. In consideration of differences in body constitution and enzyme activity, 16 mg is assumed to achieve exposure equivalent to the maximum therapeutic exposure.

Next, possible differences in the PK profile of OPC-61815 following OPC-61815 administration between healthy adults and patients with congestive heart failure were considered. Intravenous administration of OPC-61815 does not involve an absorptive process in the gastrointestinal tract, and thus a gastrointestinal absorption-related effect on heart failure can be ruled out. Once administered, OPC-61815 is likely to be hydrolyzed by alkaline and acid phosphatases in the body. These enzymes occur in a variety of organs and blood[5] and may be involved in hydrolysis. Although patients with heart failure have decreased blood flow in organs, heart failure is unlikely to affect hydrolysis (metabolism) of OPC-61815 when hydrolysis is occurring throughout the body. On the other hand, when heart failure manifests, a decrease both in blood flow in organs and in effective circulating blood volume results in a smaller volume of drug distribution for numerous drugs,[6] and the distribution volume following intravenous administration in patients with congestive heart failure may be reduced to approximately half that in healthy adults.[7] Therefore, the possibility that blood OPC-61815

concentrations in patients with congestive heart failure increase to double those in healthy adults should be anticipated. Based on these considerations, OPC-61815 administration at 16 mg and 32 mg in healthy adults appears to cause an exposure equivalent to that following administration at 8 mg and 16 mg in patients with congestive heart failure, and these doses (16 mg and 32 mg) have been selected as the clinical dose and high dose, respectively, to be used in the trial.

As described in Section 2.2.1, PK models of plasma OPC-61815 and tolvaptan concentration were created using data from the prior phase 1 studies (263-08-001, 263-09-001, and 263-10-005) to perform simulations to estimate PK parameters following a single intravenous administration of OPC-61815. First, OPC-61815 exposure was investigated. The C_{max} of OPC-61815 following simulated 1-hour intravenous administration of 32 mg OPC-61815 was as low as approximately 0.45-fold that following simulated 5-minute administration of 30 mg OPC-61815. The AUC_{24h} of OPC-61815 following simulated 1-hour intravenous administration of 32 mg OPC-61815 was approximately 1.1-fold that following simulated 5-minute administration of 30 mg OPC-61815. Given that the safety of a single 5-minute intravenous administration of 30 mg OPC-61815 has been established in healthy adults (263-08-001), both doses, 16 and 32 mg, can be administered safely provided patients are closely monitored. Next, tolvaptan exposure was investigated. The C_{max} and AUC_{24h} of tolvaptan following simulated 1-hour intravenous administration of 32 mg OPC-61815 were as low as approximately 0.45-fold and 0.18-fold, respectively, those following a single oral administration of 300 mg tolvaptan. Considering that the safety of a single oral administration of 300 mg tolvaptan has been established in healthy adults (156-03-245), 1-hour intravenous administration of 16 mg and 32 mg OPC-61815 does not appear to raise significant safety concerns from the perspective of tolvaptan exposure.

2.3 Trial Objectives

To investigate the effects of 1-hour intravenous administration of OPC-61815 at 16 and 32 mg on QT/QTc interval in healthy adult male subjects.

3 Trial Design

3.1 Type/Design of Trial

This is a single-center, randomized, double-blind, placebo- and moxifloxacin active-controlled, 4-period crossover trial in 48 healthy adult male subjects. OPC-61815 and placebo will be administered in a double-blind fashion and moxifloxacin tablets will be

administered in an open-label fashion, and the effects of 16 mg and 32 mg OPC-61815 on the QT/QTc interval will be evaluated.

The trial design schematic is shown in Figure 3.1-1.

Eligible subjects will be randomized to one of the predetermined treatment sequences prior to IMP administration on Day 1 of Period 1 (see Section 3.6.1 Randomization). Subjects will receive a single dose of OPC-61815, placebo, and moxifloxacin tablets in Periods 1 to 4 in the assigned sequence. Following the start of IMP administration, scheduled observations/examinations/assessments will be performed in a similar manner during each treatment period. A washout period of at least 6 days will be set between the days of IMP administration in a treatment period and the next treatment period. Post-treatment follow-up will be performed 6 to 8 days after the administration in Period 4. In each treatment period, subjects will be admitted to hospital on the day before IMP administration (Day −1) and discharged on Day 2.

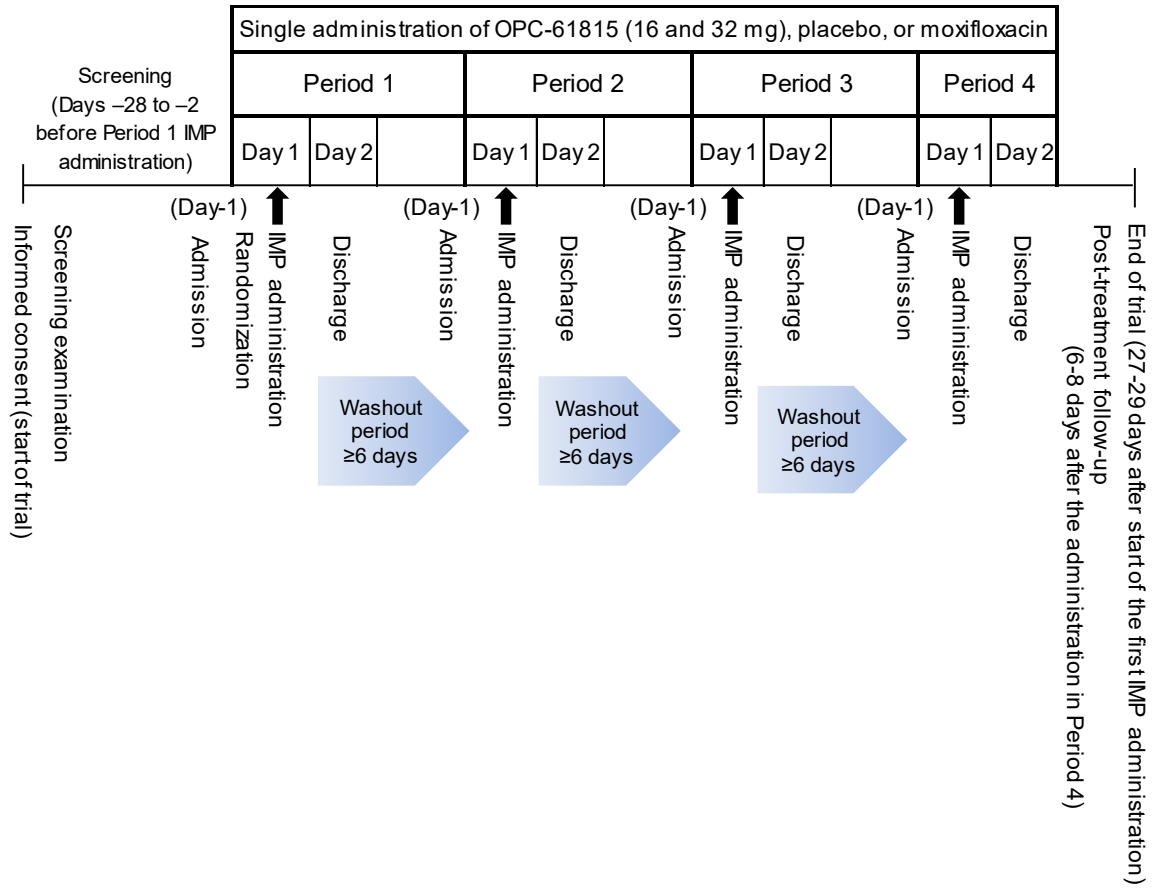

Figure 3.1-1 Trial Design Schematic

The end of trial date is counted from the start of the first IMP administration, with each washout period assumed to be 6 days.

[Rationale for trial design]

The ICH Guideline E14 states that a thorough QT/QTc study should have mechanisms to deal with potential bias, including use of randomization, appropriate blinding, and concurrent placebo control group. It also states that confidence in the ability of the study to detect QT/QTc prolongation can be greatly enhanced by the use of a concurrent positive control group. In accordance with these recommendations, this trial has a randomized, double-blind, placebo- and moxifloxacin active-controlled design. Moxifloxacin is selected as a positive control because it allows researchers to detect QT/QTc prolongation following a single administration. In addition, a crossover design allows all subjects to receive active drugs and placebo and thus has the advantage of requiring a smaller sample size than a parallel-group comparative design.

Since OPC-61815 and moxifloxacin have a half-life of <3 hours and approximately 14 hours, respectively, a washout period of ≥3 days may be sufficient for any IMP to be eliminated from the body. Considering that frequent blood samplings are planned in the trial, however, the duration of washout period was determined to be ≥6 days from the day after IMP administration.

12-lead Holter electrocardiography (ECG) that allows continuous recording of the waveform and the time will be used to evaluate the primary and secondary endpoints. In consideration of the circadian ECG variations and changes in plasma OPC-61815 concentrations, 12-lead Holter ECG will be performed until 24 hours have elapsed after start of IMP administration. In addition, considering plasma OPC-61815 concentrations, subjects will be monitored for safety until 24 hours have elapsed after start of IMP administration

Subjects will be monitored until 24 hours have elapsed after start of IMP administration on an inpatient basis so that all subjects can have ECG monitoring under as close to the same conditions as possible.

OPC-61815 is metabolized into tolvaptan in the body. A trial (156-03-245) in healthy adults evaluating the effect of orally administered tolvaptan on the QTc interval demonstrated that neither tolvaptan nor its metabolites prolong the QTc interval. This trial will therefore investigate only the effect of OPC-61815 on the QT/QTc interval.

3.2 Trial Treatments

Each subject will receive a single dose of IMP in a fasted state (see 4.2.1 Food and Beverages) in the randomly assigned sequence. OPC-61815 (16 mg and 32 mg) and placebo will be intravenously administered by 1-hour infusion. Two OPC-61815 16-mg vials will be used for administration of 32 mg OPC-61815. A moxifloxacin 400 mg tablet will be orally administered with 240 mL of water. Each subject will start to receive IMP approximately the same time of the day in all treatment periods. The allowable duration of intravenous administration of 16 mg and 32 mg OPC-61815 and placebo will be 59 to 65 minutes. The total number of IMP administration days is 4 days. Postdose monitoring will last up to Day 2 in each treatment period, and the duration of washout period starting on Day 2 is at least 6 days before IMP administration in the next treatment period. Post-treatment follow-up will be performed 6 to 8 days after IMP administration in Period 4.

[Rationale for treatment duration]

The half-life of OPC-61815 is shorter than 3 hours and plasma OPC-61815 concentrations following repeated-dose administration hardly accumulate in the steady

state. A single dose of positive control moxifloxacin sufficiently prolongs the QT/QTc interval. A single dose of each IMP should therefore allow appropriate evaluation of their effects on the QT/QTc interval.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

A total of 48 healthy male subjects age 20 to 45 years, inclusive, at time of informed consent will be enrolled in the trial.

Subjects who were scheduled to receive IMP but withdrew consent before IMP allocation and subjects considered to be unavailable for IMP administration will be replaced by standby subjects. Subjects withdrawn from the trial after IMP allocation will not be replaced.

3.3.2 Subject Selection and Numbering

Each subject will be assigned a subject identifier (site number [001] + subject number [S + 5-digit in-site serial number]) upon signing the informed consent form. The trial site will create and keep a list of all subjects who have given consent and their subject identifiers.

3.4 Eligibility Criteria

Exceptions to the eligibility criteria will not be permitted during the trial, either by the investigator or subinvestigator or by the medical advisor.

3.4.1 Informed Consent

Informed consent will be obtained from all subjects (or their guardians stipulated by the local law or legal representatives) on the basis of their free will. The informed consent form (ICF) will be approved by the same institutional review board (IRB) that approves this protocol.

Each ICF will comply with the ICH Good Clinical Practice (GCP) Guideline[8] and local regulatory requirements.

Investigators or subinvestigators may discuss the possibility that a potential subject may be allowed to enter the trial without first obtaining consent. However, a written informed consent must be obtained before initiation of any procedures that are performed for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse participation in the trial, or withdraw from the trial at any time, without justification, and their refusal or withdrawal will have no consequences for their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator or subinvestigator, an IRB-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or subinvestigator). If a trial collaborator has provided a supplemental explanation, the IRB-approved written ICF will be signed and dated by the trial collaborator as well. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator or subinvestigator.

Subjects may be asked to sign additional ICFs, if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make an informed and voluntary decision on their participation in the trial.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1	Japanese male subjects age 20 to 45 years, inclusive, at time of informed consent
2	Body mass index (BMI) (body weight in kilogram / [height in meter]^2) of at least 18.5 kg/m^2 and less than 25.0 kg/m^2 based on the results of the screening examination
3	Judged by the investigator or subinvestigator to be capable of providing written informed consent prior to start of any trial-related procedures and capable of complying with all the requirements for this trial

[Rationale for inclusion criteria]

1 Age: The lower limit of 20 years is the age at which an individual is legally regarded as an adult capable of taking responsibility for consent. The upper limit of 45 years is based on the consideration that individuals older than 45 years are likely to develop concurrent diseases.
Race: Only Japanese subjects will be included because the trial will be conducted for the purpose of applying for a marketing approval in Japan.
Sex: Only men will be included, because the possibility of pregnancy does not need to be considered in men.

2 In order to reduce interindividual PK variations.

3 In order to conduct the trial in an ethically appropriate manner.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1. The day of IMP administration mentioned in these criteria denotes the scheduled administration day. If clinical laboratory tests are performed again at the discretion of the investigator or subinvestigator, they should be recorded according to the trial site's procedure.

Subjects excluded as a result of positive urine drug, cotinine, or breath alcohol test, a failure to appropriately evaluate ECGs (exclusion criteria 1 to 5), or falling under exclusion criteria 21, 22, or 24 cannot be rescreened. However, subjects excluded as a result of falling under other exclusion criteria may be rescreened if any changes in the relevant condition are observed. For rescreening, the subject must sign a new ICF, be assigned a new subject identifier, and undergo all screening examinations/assessments again.

Table 3.4.3-1 Exclusion Criteria

1	Subjects with a medical history of convulsive disorder, long QT syndrome (including family history), syncope during swimming, or any other type of syncope or cryptogenic loss of consciousness
2	Subjects with a serum electrolyte abnormality (hypokalemia, hypomagnesemia, hypocalcemia, etc.)
3	Subjects with a family history of sudden death
4	Subjects with a history of heart disease such as hypertension, atherosclerosis, heart failure, bradycardia, or stroke, or who are using a pacemaker
5	Subjects with 2 or more of the following abnormalities in 3 tests of 12-lead ECG and 2 or more additional abnormalities in re-testing performed 1 hour after the first series of tests at the screening examination or on the day before Period 1 IMP administration (Day −1) • PR interval of >220 msec • QRS interval of >120 msec • QTcF of <320 msec or >450 msec • Atrial fibrillation or atrial flutter • Other worrisome cardiac findings
6	Subjects who have received any other IMP in another clinical trial within 120 days prior to Period 1 IMP administration
7	Subjects who have undergone blood collection (eg, blood donation) of >200 mL within 30 days, >400 mL within 90 days, or >1200 mL within 1 year prior to Period 1 IMP administration
8	Subjects who have consumed any of the following products within the corresponding specified time prior to Period 1 IMP administration • Products containing St John's wort (Hypericum perforatum): Within 14 days prior to Period 1 IMP administration • Products containing grapefruit, Seville orange, or star fruit: Within 7 days prior to Period 1 IMP administration • Food or beverages containing alcohol or caffeine: Within 1 day prior to Period 1 IMP administration
9	Subjects who have taken any prescription drugs, OTC drugs, Chinese herbal remedies, or vitamin supplements within 14 days or antibiotics within 30 days prior to Period 1 IMP administration

Table 3.4.3-1	Exclusion Criteria
10	Subjects who have been exposed to any substance known to stimulate production of liver microsomal enzymes (eg, occupational exposure to pesticides or organic solvents) within 30 days prior to Period 1 IMP administration
11	Subjects who have used any tobacco products, nicotine replacement therapy, or electronic cigarettes, or who have been exposed to second-hand smoke on a daily basis, within 60 days prior to Period 1 IMP administration, or who test positive in urine nicotine test at the screening examination
12	Sexually active men who: • Are unable or unwilling to either use 2 types of approved contraception methods or remain abstinent during the trial and for 30 days after final IMP administration. If employing birth control, use 2 of the following approved methods of birth control: vasectomy, tubal ligation, intrauterine device, birth control pill, condom with spermicide, occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide. • Plan to donate sperm within 30 days after final IMP administration.
13	Subjects with a history of a clinically significant abnormality, or for whom a clinically significant abnormality is observed in the results of the screening examination, and the investigator, subinvestigator, or sponsor judges that the abnormality could place the subject at risk or affect evaluation of drug absorption, distribution, metabolism, or excretion. Such abnormalities include, but are not limited to, a history or current symptoms of cardiac, hepatic, renal, nervous system, endocrine, gastrointestinal, respiratory, and hematic immune diseases/disorders.
14	Subjects with a history of clinically significant drug or alcohol abuse
15	Subjects with a history or current condition of hepatitis or acquired immunodeficiency syndrome (AIDS), or a positive test result for any of the following: Hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibody, AIDS antigen/antibody, or syphilis
16	Subjects with a history of severe drug allergy or hypersensitivity to any of the following drugs: • Any ingredients of OPC-61815 or tolvaptan • Compounds containing benzazepine (mozavaptan hydrochloride, benazepril hydrochloride) • Quinolone antibiotics, including moxifloxacin
17	Subjects who have a positive test result in breath alcohol test or urine drug test for detection of substance abuse at the screening examination or on the day before Period 1 IMP administration (Day −1)
18	Subjects with a history of serious hemorrhage or bleeding tendency
19	Subjects with blood collection difficulty
20	Subjects with supine resting systolic blood pressure of >140 mmHg or <90 mmHg or supine resting diastolic blood pressure of >80 mmHg or <40 mmHg at the screening examination or on the day before Period 1 IMP administration (Day −1) (see Section 3.7.5.4 Vital Signs (Blood Pressure, Pulse Rate, and Body Temperature))
21	Subjects with supine resting pulse rate of >90 bpm or <45 bpm at the screening examination or on the day before Period 1 IMP administration (Day −1) (see Section 3.7.5.4 Vital Signs (Blood Pressure, Pulse Rate, and Body Temperature)).
22	Subjects who are currently taking an antiarrhythmic agent of Class IA (quinidine, procainamide, etc.) or Class III (amiodarone, sotalol, etc.)
23	Subjects with a history of serious psychological disorder whose participation in the clinical trial is judged to be inappropriate by the investigator or subinvestigator
24	Subjects who are otherwise judged by the investigator or subinvestigator to be inappropriate for participation in the clinical trial

[Rationale for exclusion criteria]
1 to 5 Based on exclusion criteria recommended in the ICH Guideline E14.
6 In reference to the Standards for Intervals During Which Subjects Should Refrain from Participating in a Clinical Trial[9] proposed by the Japan Association of Contract Institutes for Clinical Pharmacology.
7 In reference to the blood sampling criteria[10] proposed by the New Blood Programme Advisory Committee.
8 It is reported that some food products containing St John's wort induce drug-metabolizing enzymes such as CYP3A4, and that grapefruit, Seville orange, and star fruit inhibit CYP3A4. Based on these reports, this criterion is used to avoid their possible effects on the PK of IMP.
9 to 11 To avoid their possible effects on the PK of IMP.
12 to 22 For safety reasons.
23 and 24 For general safety and ethical reasons.

3.5 Endpoints

3.5.1 Primary Endpoint(s)

Time-matched difference between the OPC-61815 and placebo data in change from baseline for QTcF in 12-lead Holter ECG

3.5.2 Secondary Endpoint(s)

12-lead Holter ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval) and ECG waveform patterns

3.5.3 Pharmacokinetic Endpoints

Plasma concentrations and pharmacokinetic parameters of OPC-61815 free form and tolvaptan

3.5.4 Safety Endpoints

Adverse event reporting, clinical laboratory assessments, physical examination, vital signs (blood pressure, pulse rate, and body temperature), body weight, and 12-lead ECG

3.6 Measures to Minimize/Avoid Bias

3.6.1 Randomization

Eligible subjects will be randomized at the equal ratio to one of different sequences of 4 treatments (16 mg OPC-61815, 32 mg OPC-61815, placebo, and moxifloxacin). The sequences will be determined so that each treatment will be given equally in each treatment period. The details are provided in a separate document.

3.6.2 Blinding

In this trial, OPC-61815 and placebo will be administered in a double-blind fashion and moxifloxacin tables will be administered in an open-label fashion.

The lyophilized OPC-61815 and placebo in vials are similar in their appearance but the two solutions will be distinguishable in appearance once prepared: Foam may be seen immediately after preparation but will disappear in a certain period of time. To maintain blindedness of all trial site staff participating in assessment during the trial, the trial site will appoint a third person (non-blinded staff) who is responsible for preparation of IMP.

The person responsible for IMP preparation should be qualified with a pharmacist license for drug preparation and appointed at the trial site. The details on procedures of IMP preparation and maintenance of blindness at the trial site where the non-blinded staff responsible for IMP preparation is appointed will be specified separately in pharmacy manual. The non-blinded staff responsible for IMP preparation is required to maintain confidentiality of information related to the preparation of the IMP solution. Any queries related to IMP are to be addressed to the contact person specified in the manual rather than the trial monitor.

To maintain access to IMP throughout the trial, the trial site may appoint a deputy person responsible for IMP preparation (non-blinded staff).

3.6.3 Reading of 12-Lead Holter Electrocardiograms

The ICH Guideline E14 recommends blinded ECG assessment by a few skilled readers at the central ECG laboratory. It also states that the degree of inter- and intra-reader variability should be established by having the assessors reread a subset of the data under blinded conditions. In this trial, a few skilled readers will read ECGs at the central ECG laboratory and the assessors will reread a subset of the data to avoid 12-lead Holter ECG reading bias.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1. Acceptable windows for postdose examinations/assessments (for all treatment periods) are shown in Table 3.7-2.

Table 3.7-1 Schedule of Assessments

	Visits	Hospitalization at Trial Site												Visits
	Screening	Day Before Administration	Period 1, 2, 3, and 4 (Washout Period: At least 6 days)										At Withdrawal	Post-treatment follow up
Day	Day -28 to Day -2	Day -1	Day 1									Day 2		
Time From Start of Administration (hours)			Predose	0 Start of Infusion	0.5	1 End of Infusion	1.5	2	3	4	6	12 / 24		
Informed consent	X													
Subject demographics	X													
Urine drug and cotinine, and breath alcohol tests	X	X												
Infectious disease screening	X													
Randomization[a]			X											
IMP administration				X										
Trial Assessments														
12-Lead Holter ECG			X[d]			X	X	X	X	X	X	X		
Blood collection for plasma concentration measurement			X			X	X	X	X	X	X	X	X[e]	
Clinical laboratory test[b]	X		X			X					X	X	X	X
Physical examination	X	X	X			X		X		X			X	X	X
Vital signs (blood pressure, pulse rate, temperature)[c]	X	X	X		X	X		X		X	X		X	X	X
Body weight	X		X			X							X	X	X
12-Lead ECG	X	X	X			X		X		X	X		X	X	X
Adverse events	←													→
Concomitant medication/therapy	←													→

Note: This table shows the schedule of assessments. For a summary of the assessment items and timepoints by trial period and day, refer to Section 3.7.3 Schedule of Assessments.

[a]Performed only on Day 1 of Period 1.

[b]Of the blood biochemistry tests, only serum sodium and potassium will be measured at 6 and 12 hours postdose.

[c]Only blood pressure and pulse rate will be measured at 30 minutes, and 1, 2, 4, and 6 hours postdose.

[d]Performed at 1 hour, 30 minutes, and 15 minutes prior to IMP administration.

[e]Performed at the time of withdrawal during hospitalization.

Table 3.7-2 Acceptable Windows for Postdose Examinations/Assessments (for All Treatment Periods)

Examination/Assessment	Time point (time from start of IMP administration)		Acceptable window
PK blood sampling (performed after completion of resting 12-lead Holter ECG)	Day 1	1 hour	Within 2 minutes after end of IMP administration[a]
		1.5 hours	Specified time point + 2 minutes
		2 hours	Specified time point + 3 minutes
		3 hours	Specified time point + 5 minutes
		4 hours	Specified time point + 10 minutes
		6 and 12 hours	Specified time point + 15 minutes
	Day 2	24 hours	Specified time point + 30 minutes
Clinical laboratory tests	Day 1	1, 6, and 12 hours	Specified time point ± 30 minutes
	Day 2	24 hours	Specified time point ± 1 hour
Physical examination	Day 1	1, 2, and 4 hours	Specified time point ± 20 minutes
	Day 2	24 hours	Specified time point ± 1 hour
Vital signs	Day 1	30 minutes	20-45 minutes after start of IMP administration
		1, 2, 4, and 6 hours	Specified time point ± 30 minutes
	Day 2	24 hours	Specified time point ± 1 hour
Body weight	Day 2	24 hours	Specified time point ± 1 hour
12-lead ECG	Day 1	1, 2, 4, and 6 hours	Specified time point ± 30 minutes
	Day 2	24 hours	Specified time point ±1 hour

[a] For moxifloxacin, specified time point + 2 minutes

3.7.1 General Inpatient Procedures

Subjects will be instructed to rest as much as possible and avoid strenuous exercise during hospitalization.

IMP administration may cause dehydration. Subjects will be instructed to drink an appropriate amount of water to ensure their safety.

Subjects will take a moxifloxacin 400-mg tablet with 240 mL of water and then undergo an oral check to see if the drug was appropriately consumed. Restroom visits must be supervised during the 4 hours postdose and should be brief (<10 minutes). In addition, during the 4-hour period after oral dosing, the subject's toilet use must be supervised to prevent self-induced emesis resulting in loss of the oral dose.

3.7.2 Dietary Requirements

During hospitalization, subjects must not consume foods or beverage other than those provided by the trial site. If the mealtime coincides with a time point for

examination/assessment or blood sampling, subjects will undergo the examination/assessment or blood sampling before having a meal.

3.7.3 Schedule of Assessments

3.7.3.1 Informed Consent

Prior to screening examination, the investigator or subinvestigator will obtain written informed consent from the subject. After obtaining consent from the subject, the investigator or subinvestigator will perform the screening examination.

3.7.3.2 Screening

After obtaining informed consent, the investigator or subinvestigator will assign a subject identifier to each subject according to Section 3.3.2 Subject Selection and Numbering. Subjects will visit the trial site at any date and time that is convenient to them between 28 and 2 days before Period 1 IMP administration and undergo the following examinations/assessments for eligibility assessment. The results of eligibility assessment will be recorded in the case report form (CRF). If a subject is judged to be eligible for the trial despite the presence of some abnormality, the reason for the judgment will be documented in the medical records and other relevant documents.

For rescreened subjects, the previous subject identifier (S + 5-digit in-site serial number) will also be recorded in the CRF.

- Subject demographics (birth date, complications, medical history [within 1 year before informed consent])
- Height, body weight, and body mass index (BMI)
  Height will be measured to the first decimal place in centimeters. If height is measured to the second decimal place, the measurement will be rounded off to the first decimal place. BMI will be calculated based on height and body weight at screening using the following formula: BMI = body weight (kg) / height $(m)^2$.
- Urine drug test, urine cotinine test, and breath alcohol test
- Infectious disease screening
- Clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- ECG (standard triplicate 12-lead ECG)
- AEs
- Concomitant medications/therapies

3.7.3.3 Day Before IMP Administration (Day −1) in Period 1

Subjects and standby subjects who are judged to be eligible based on the screening results will be admitted to the trial site on the day before Period 1 IMP administration (Day −1). They will undergo the following examinations/assessments and be rechecked against the inclusion and exclusion criteria. The date and results of recheck will be recorded in the screening list and the subject enrollment list.

- Urine drug test, urine cotinine test, and breath alcohol test
- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature)
- ECG (standard triplicate 12-lead ECG)
- AEs
- Concomitant medications/therapies

3.7.3.4 Day 1 of Period 1

The investigator or subinvestigator will select subjects who are judged to be eligible based on the screening results and whose condition up to immediately before IMP administration indicates that they can safely receive IMP, assign them each a randomization number in the ascending order of the subject identifier, and randomize them to treatments. The date and number of randomization will be recorded in the CRF. Standby subjects will be discharged from the trial site once all the subjects to receive IMP administration are determined.

Following randomization, subjects will receive IMP.

The following examinations/assessments will be performed.

1) Within 3 hours before IMP administration
- Blood sampling for plasma drug concentration measurement
- Clinical laboratory tests (hematology, biochemistry, and urinalysis [urinalysis will take place after waking up and before IMP administration])
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight

2) Within 2 hours before IMP administration
- ECG (12-lead ECG)

3) Within 1 hour, 30 minutes, and 15 minutes before IMP administration

- ECG (12-lead Holter ECG)

4) Start of IMP administration (a 1-hour intravenous administration of an injection or a single administration of a tablet)

5) Examinations/assessments after start of IMP administration

- Blood sampling for plasma drug concentration measurement: 1, 1.5, 2, 3, 4, 6, and 12 hours after start of IMP administration
- ECG (12-lead Holter ECG): 1, 1.5, 2, 3, 4, 6, and 12 hours after start of IMP administration
- Clinical laboratory tests
  Hematology, biochemistry, and urinalysis: 1 hour after start of IMP administration
  Serum electrolytes (sodium and potassium only): 6 and 12 hours after start of IMP administration (blood sampling will take place concurrently with that for plasma drug concentration measurement)
- Physical examination: 1, 2, and 4 hours after start of IMP administration
- Vital signs (blood pressure and pulse rate only): 30 minutes, 1, 2, 4, and 6 hours after start of IMP administration
- ECG (12-lead ECG): 1, 2, 4, and 6 hours after start of IMP administration
- AEs
- Concomitant medications/therapies

3.7.3.5 Day 2 of Period 1

The following examinations/assessments will be performed at 24 hours after start of IMP administration. Subjects without safety problems will be discharged from the trial site.

- Blood sampling for plasma drug concentration measurement
- ECG (12-lead Holter ECG)
- Clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight
- ECG (12-lead ECG)
- AEs
- Concomitant medications/therapies

3.7.3.6 Day Before IMP administration (Day −1) in Periods 2, 3, and 4

Subjects will visit the trial site for the following examinations/assessments. Subjects whose condition indicates that they can safely receive IMP will be admitted to the trial site.

- Urine drug test, urine cotinine test, and breath alcohol test
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- ECG (12-lead ECG)
- AEs
- Concomitant medications/therapies

3.7.3.7 Day 1 of Periods 2, 3, and 4

The investigator or subinvestigator will perform the following examinations/assessments on subjects whose condition up to immediately before IMP administration indicates that they can safely receive IMP.

1) Within 3 hours before IMP administration
- Blood sampling for plasma drug concentration measurement
- Clinical laboratory tests (hematology, biochemistry, and urinalysis [urinalysis will take place after waking up and before IMP administration])
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight

2) Within 2 hours before IMP administration
- ECG (12-lead ECG)

3) Within 1 hour, 30 minutes, and 15 minutes before IMP administration
- ECG (12-lead Holter ECG)

4) Start of IMP administration (a 1-hour intravenous administration of an injection or a single administration of a tablet)

5) Examinations/assessments after start of IMP administration
- Blood sampling for plasma drug concentration measurement: 1, 1.5, 2, 3, 4, 6, and 12 hours after start of IMP administration

- ECG (12-lead Holter ECG): 1, 1.5, 2, 3, 4, 6, and 12 hours after start of IMP administration
- Clinical laboratory tests
  Hematology, biochemistry, and urinalysis: 1 hour after start of IMP administration
  Serum electrolytes (sodium and potassium only): 6 and 12 hours after start of IMP administration
- Physical examination: 1, 2, and 4 hours after start of IMP administration
- Vital signs (blood pressure and pulse rate only): 30 minutes, 1, 2, 4, and 6 hours after start of IMP administration
- ECG (12-lead ECG): 1, 2, 4, and 6 hours after start of IMP administration
- AEs
- Concomitant medications/therapies

3.7.3.8 Day 2 of Periods 2, 3, and 4

The following examinations/assessments will be performed 24 hours after start of IMP administration. Subjects without safety problems will be discharged from the trial site.

- Blood sampling for plasma drug concentration measurement
- ECG (12-lead Holter ECG)
- Clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight
- ECG (12-lead ECG)
- AEs
- Concomitant medications/therapies

3.7.3.9 Withdrawal Examination

Subjects who are withdrawn from the trial following any IMP administration will undergo the following observations/examinations. If a trial withdrawal takes place while the subject is not hospitalized, withdrawal examination is unnecessary and post-treatment follow-up will be performed instead.

- Blood sampling for plasma drug concentration measurement
- Clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Physical examination

- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight
- ECG (12-lead ECG)
- AEs
- Concomitant medications/therapies

3.7.3.10 Post-treatment Follow-up

Subjects will visit the trial site at any date and time that is convenient to them between 6 and 8 days after the final IMP administration and undergo the following examinations/assessments. Subjects who are withdrawn from the IMP administration for any reason will also undergo the following examinations/assessments between 6 and 8 days after withdrawal.

- Clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight
- ECG (12-lead ECG)
- AEs
- Concomitant medications/therapies

3.7.3.11 Post-trial Follow-up

Subjects will be followed up as described in Section 5.7 Follow-up of Adverse Events.

3.7.4 Prior and Concomitant Medications

The investigator or subinvestigator will record all medications (drug name, purpose of use, dose, frequency, route of administration, and start and end dates of treatment) and therapies (therapy name, purpose of use, and start and end dates of treatment) taken by the subject from 60 days prior to Day 1 of Period 1 through post-treatment follow-up (end of trial) in the CRF.

3.7.5 Safety Assessments

3.7.5.1 Adverse Events

Refer to Section 5 Reporting of Adverse Events for the methods and timing for assessing, recording, and analyzing AEs.

3.7.5.2 Clinical Laboratory Assessments

3.7.5.2.1 Clinical Laboratory Tests

Clinical laboratory tests listed in Table 3.7.5.2-1 will be performed at the scheduled time points (see Table 3.7-1 and Table 3.7-2) according to the procedure specified by the trial site. To ensure subject safety, serum sodium and potassium concentrations will be determined at 6 and 12 hours after start of IMP administration on Day 1 in each treatment period. Blood sampling for serum sodium and potassium will take place concurrently with that for plasma drug concentration measurement. The investigator or subinvestigator will promptly review the test results. The dates and times of blood and urine samplings will be recorded in the CRF. The test results and reference values will be reported directly to the sponsor in the electronic format, and recording in the CRF is unnecessary.

Table 3.7.5.2-1 Clinical Laboratory Assessments

Hematology:	Serum Chemistry:
Hematocrit	Protein, total
Hemoglobin	Albumin
Platelet count	Bilirubin, total
Mean corpuscular hemoglobin concentration (MCHC)	Aspartate aminotransferase (AST)
Mean corpuscular volume (MCV)	Alanine aminotransferase (ALT)
Red blood cell count	Alkaline phosphatase (ALP)
White blood cell count with differential	γ-Glutamyl transferase (γ-GTP)
	Lactic dehydrogenase (LDH)
Urinalysis:	Creatine kinase (CK [CPK])
Specific gravity	Glucose
pH	Cholesterol, total
Qualitative testing	Triglycerides
Protein	Urea nitrogen
Glucose	Creatinine
Occult blood	Uric acid
Ketones	Serum electrolytes
Bilirubin	sodium (Na), magnesium (Mg)
Urobilinogen	potassium (K), calcium (Ca)
	chloride (Cl)

3.7.5.2.2 Infectious Disease Screening

The following tests will be performed at screening according to the procedure specified by the trial site. The date and time of blood sampling and test results will be recorded in the CRF.

- Hepatitis B surface antigen (HBsAg)
- Anti-hepatitis C virus (HCV) antibody
- Human immunodeficiency virus (HIV) antigen/antibody
- Syphilis

3.7.5.2.3 Urine Drug Test, Urine Cotinine Test, and Breath Alcohol Test

The following tests will be performed at the time points specified in Table 3.7-1 according to the procedure specified by the trial site. The date and time of urine sampling, date and time of test, and test results will be recorded in the CRF.

- Urine drug test (amphetamine, barbiturates, benzodiazepines, cannabinoid, cocaine, opiates, and phencyclidine)
- Urine cotinine test
- Breath alcohol test

3.7.5.3 Physical Examination

Physical examinations will be performed at the scheduled time points (see Table 3.7-1 and Table 3.7-2). The head, ears, eyes, nose and pharynx, chest, abdomen, urogenital organs, limbs, nervous system, and skin and mucous membrane will be examined.

The date and results of the screening physical examination will be recorded in the CRF and only the dates of post-screening physical examinations will be recorded in the CRF. Any clinically relevant physical findings that are noted after screening but not at screening will be identified as AEs and recorded in the CRF.

It is preferable for the same physician to perform all physical examinations for any individual subject throughout the course of the trial.

3.7.5.4 Vital Signs (Blood Pressure, Pulse Rate, and Body Temperature)

Vital signs will be measured at the scheduled time points (see Table 3.7-1 and Table 3.7-2). Blood pressure (diastolic and systolic) and pulse rate will be measured in the supine position using a well-maintained instrument after the subject has rested for at least 3 minutes. Blood pressure and pulse rate measurement at each time point after start of IMP administration will take place after completion of 12-lead Holter ECG and blood sampling. Blood pressure and pulse rate measurement at 30 minutes, 1 and 2 hours after start of IMP administration will take place by the time when the subject starts to rest for the next 12-lead Holter ECG.

Whether or not the measurement was performed, together with the date and time of measurement and the blood pressure and pulse rate measurements will be recorded in the CRF.

Subjects whose blood pressure or pulse rate measurement at screening or at admission meets the relevant exclusion criteria but is not considered clinically meaningful will then have their blood pressure or pulse rate measured in triplicate at intervals of 10 minutes. Those with 2 of 3 measurements not meeting the relevant exclusion criteria will be enrolled in the trial.

Axillary temperature will be measured to the first decimal place in Celsius using a well-maintained thermometer. Whether or not the measurement was performed, together with the date and time of measurement and the temperature measurement will be recorded in the CRF. When the thermometer uses measures to the second or more decimal place, the reading is rounded to the first decimal place.

3.7.5.5 Body Weight

Body weight will be measured at the scheduled time points (see Table 3.7-1 and Table 3.7-2). Subjects must urinate at least once after waking up. After minimizing the effect of bowel movement and clothing-related variations, body weight will be measured using a well-maintained scale. The date and time of measurement and body weight measurement in kilograms (to the first decimal place) will be recorded in the CRF. When the scale uses measures to the second or more decimal place, the reading is rounded off to the first decimal place.

3.7.5.6 12-Lead Electrocardiogram Assessments

The investigator or subinvestigator will globally assess whether ECG findings are normal or abnormal based on ECG charts and record the assessment result, and if abnormal, together with the abnormal finding, in the CRF. The date and time of measurement (if done in triplicate, only the first measurement), heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval are all to be recorded in the CRF. As a general rule, an abnormal finding will be identified as an AE; however, for an abnormal finding that the investigator or subinvestigator does not judge to be an AE, the reason for the judgment will be recorded in the source documents.

Refer to Section 3.8.3 Individual Subject Discontinuation for the procedure for trial discontinuation due to abnormal 12-lead ECGs.

3.7.5.6.1 Screening Examination and Day Before IMP Administration in Each Period (Day −1)

Resting 12-lead ECG will be performed at the scheduled time points (see Table 3.7-1 and Table 3.7-2) using a well-maintained standard 12-lead electrocardiograph provided by the trial site according to the procedure specified by the trial site.

12-lead ECG will be performed in triplicate with electrodes placed at the same places at all time points wherever possible.

3.7.5.6.2 Days 1 and 2 in Each Period and Post-treatment Follow-up

Resting 12-lead ECGs will be performed at the scheduled time points (see Table 3.7-1 and Table 3.7-2) using a well-maintained standard 12-lead electrocardiograph provided by the trial site or a 12-lead Holter electrocardiograph supplied by the central ECG laboratory according to the procedure specified by the trial site.

12-lead ECG will be performed once, not in triplicate, with electrodes placed at the same places at all time points wherever possible.

3.7.6 Pharmacokinetic/Pharmacodynamic Assessments

3.7.6.1 Pharmacokinetic Assessments

3.7.6.1.1 Pharmacokinetic Blood Samples

1) Blood sampling/measurement method

Blood samples will be collected at the scheduled time points as shown in Table 3.7-1 for all treatments with OPC-61815, placebo, and moxifloxacin to measure plasma concentrations of OPC-61815 free form and tolvaptan. Concentrations of moxifloxacin and additional metabolites that are not identified in the protocol may also be analyzed if new information becomes available.

All plasma samples will be shipped to the bioanalytical laboratory. Detailed handling and shipping instructions are provided in Appendix 1. Whether or not blood was collected, and the date and time of blood sampling will be recorded. The bioanalytical laboratory will report the analysis results directly to the sponsor. Recording of analysis results in the CRF is unnecessary.

After unblinding, the bioanalytical laboratory will submit the bioanalytical data, or table(s) of drug concentrations, in electronic format to the sponsor.

2) Rationale for blood sampling schedule

The following time points for blood sampling were determined for Day 1 according to the results of 1-hour OPC-61815 injection simulation based on the population PK models developed using the results of a single intravenous dose trial of OPC-61815 in healthy adults (263-08-001), a repeated intravenous dose trial of OPC-61815 in healthy adults (263-09-001), and an intravenous dose trial on rate of injection of OPC-61815 in healthy adults (263-10-005), as well as in consideration of feasibility, so that necessary PK parameters of OPC-61815 free form and tolvaptan can be

calculated: 1 predose time point; estimated t_{max} of OPC-61815 free form (1 hour after start of administration) by simulation and 3 time points (1, 1.5, and 2 hours after start of IMP administration) around estimated t_{max} of tolvaptan by simulation; 3 time points (3, 4, and 6 hours after start of IMP administration) that are estimated to be in the elimination phase of OPC-61815 free form; and 3 time points (6, 12, and 24 hours after start of IMP administration) that are estimated to be in the elimination phase of tolvaptan. Since, in accordance with the Questions and Answers 3-2 in the ICH Guideline E14, this trial should be conducted uniformly following the specified trial procedures, blood samples will also be collected when moxifloxacin is administered in an open-label fashion.

3.7.6.1.2 Pharmacokinetic Urine Samples

PK urine samples will not be collected.

3.7.6.2 Pharmacodynamic Assessments

3.7.6.2.1 12-Lead Holter Electrocardiogram Assessments

1) Procedure

12-lead Holter ECG will be performed using a 12-lead Holter electrocardiograph supplied by the central ECG laboratory according to the procedure specified by the central ECG laboratory.

Subjects will be connected to a 12-lead Holter electrocardiograph prior to ECG recording performed at 1 hour before IMP administration on Day 1 in each treatment period. To standardize the test conditions for all time points for assessment, subjects will remain at rest in the supine position (they are conscious but must remain silent) for approximately 10 minutes from 15 minutes before the specified time point and will then continue in the resting state in the supine position (they must remain motionless and nobody should speak to them) for approximately 5 minutes from 5 minutes before the specified time point. Electrodes will be placed at the same places at all time points wherever possible. If the time point for 12-lead Holter ECG coincides with a time point for examination/assessment or blood sampling, subjects will undergo 12-lead Holter ECG before the examination/assessment or blood sampling.

The dates and times of start and end of ECG recording and the dates and times of start and end of the resting state will be recorded in the CRF. The time displayed on an appropriate clock in the trial site will be recorded.

2) Data transfer
The trial site will send all 12-lead Holter ECG data to the central ECG laboratory according to a separately specified procedure.

3) Retrieval of ECG analysis results
The sponsor will receive from the central ECG laboratory the analysis results, or 12-lead Holter ECG analysis report (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval), and ECG waveform patterns. Recording of ECG analysis results in the CRF is unnecessary.

4) Assessments
The investigator or subinvestigator will globally assess whether ECG findings are normal or abnormal based on the 12-lead Holter ECG analysis report, and record whether or not an ECG was performed, the date of ECG, and normal/abnormal assessment (with the finding if abnormal) in the source documents. As a general rule, an abnormal finding will be identified as an AE; however, for an abnormal finding that the investigator or subinvestigator does not judge to be an AE, the reason for the judgment will be recorded in the source documents.

3.7.7 Genetic Assessments

No genetic assessments are planned in this trial.

3.7.8 Future Biospecimen Research Samples

No future biospecimen research assessments are planned in this trial.

3.7.9 End of Trial

The end of trial date is defined as the end date of post-treatment follow-up. If the subject is lost to follow up, it will be the date of the final contact attempt.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

In the event of sponsor termination or suspension of the trial for any reason, prompt notification will be given to the head of the trial site and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

The sponsor, investigator, or the IRB has the right to terminate the participation of a particular trial site, if necessary, due to lack of subject enrollment, noncompliance with

the protocol, or if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP. The head of the trial site shall promptly notify the sponsor, if the termination of the trial was determined by the investigator or the IRB at the trial site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation/Interruption During a Treatment Period

After the first dose of IMP, a subject may permanently stop or interrupt treatment during any of the treatment periods for a variety of reasons. Treatment discontinuation or interruption in any treatment period may be initiated by a subject or may become medically necessary due to AEs, required treatment with a prohibited medication or therapy, or for other reasons, as determined by the investigator or subinvestigator. Even when a subject discontinues or interrupts treatment during a treatment period, the subject may continue participation in the trial, if the investigator or subinvestigator decides that the subject is eligible for resuming treatment or receiving IMP for the remaining periods and if the subject is willing to continue the trial.

3.8.3.2 Treatment Discontinuation (Withdrawal)

After the first dose of IMP, a subject may permanently stop treatment for a variety of reasons. Treatment discontinuations may be initiated by a subject or may become medically necessary due to AEs, required treatment with a prohibited medication or therapy, or for other reasons, as determined by the investigator or subinvestigator. Any subject who is unwilling to continue the trial after discontinuing treatment during a treatment period (see Section 3.8.3.1) must be withdrawn from the trial. Subjects who withdrew after the start of the IMP administration should be encouraged to complete all early termination (ET) assessments as soon as possible after withdrawal.

If any of the following AEs occur, the subject must be withdrawn from the trial for safety reasons after discontinuation of IMP:

- Occurrence of severe drug hypersensitivity
- Occurrence of severe AEs of special interest (feeling abnormal, feeling hot, erythema, hyperhidrosis, pruritus, rash, urticaria, nausea, epigastric discomfort, dyspnoea)
- AST or ALT ≥3 times the upper limit of normal (ULN)
- ≥12 mEq/L increase in serum sodium concentration within 24 hours of IMP administration compared to baseline
- A serum sodium concentration of ≥155 mEq/L

- Regarding 12-lead ECG findings the day before IMP administration (Day −1) in Periods 2, 3, and 4, QTcF interval of <320 msec or >450 msec observed in at least 2 of 3 ECG recordings performed 1 hour after preceding observation of QTcF interval in either range in at least 2 of 3 ECG recordings
- Regarding 12-lead ECG findings after start of IMP administration in each period, QTcF interval of >500 msec observed in an ECG recording 1 hour after preceding observation of QTcF interval in the same range (if a 12-lead ECG recording is originally scheduled 1 hour after the first recording, the scheduled test constitutes the re-examination.)

3.8.3.3 Documenting Reasons for Discontinuation

All subjects have the right to withdraw from the trial and the investigator or subinvestigator can discontinue a subject's participation in the trial at any time, if medically necessary. In addition, subjects meeting the following criteria must be withdrawn from the trial. Only one reason for discontinuation (the main reason) can be recorded in the CRF:

- Investigator/subinvestigator or subject decision (AE)
  - AEs requiring discontinuation
  - AEs meeting the criteria specified in Section 3.8.3.2 Treatment Discontinuation (Withdrawal)
- Investigator/subinvestigator decision (other than AE)
- Major protocol deviation (other than non-compliance with IMP)
  - Failure to meet the inclusion criteria or coming under the exclusion criteria
- Trial terminated by sponsor
- Withdrawal of consent by subject (if confirmed not related to an AE)
- Lost to follow-up

If the subject discontinues IMP due to an AE, the investigator, subinvestigator, or other trial personnel will make every effort to follow the event until it has resolved or stabilized or the subject is lost to follow-up or dies. Follow-up procedures in Section 5.7 Follow-up of Adverse Events must be followed. If there are withdrawals prior to randomization, subjects may be replaced as described in Section 3.3.1 Number of Subjects and Description of Population.

3.8.3.4 Withdrawal of Consent

All subjects have the right to withdraw their consent for further participation in the trial at any time without sustaining a disadvantage. Subjects cannot withdraw consent to the use of data already collected as part of the trial, but only for future participation.

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of caution as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be understood, documented, and managed to protect the rights of the subject and ensure the integrity of the trial.

Subjects who withdrew after the start of the IMP administration should be encouraged to complete all ET assessments as soon as possible after withdrawal.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented (ie, subject signs an ICF), but who is not randomized or assigned trial treatment.

Screen failure subjects are permitted to be rescreened. In the event that the subject is rescreened for trial participation, a new ICF must be signed, a new subject identifier assigned, and all screening procedures repeated.

For each screen failure subject, the following information shall be documented in the ICF:

- Visit date
- Date of consent
- Screened date
- Birth date
- Result of eligibility assessment (indicate the article number of the criterion the subject failed to meet)
- Date of screen failure assessment
- Reason for screen failure assessment

3.10 Definition of Completed Subjects

The evaluation period is defined as the time period during which the subject is evaluated for primary and secondary objectives of the trial regardless of whether all IMP doses were administered. Subjects who are evaluated at the last scheduled visit during the

evaluation period will be defined as trial completers. For the purposes of this trial, subjects who complete the examinations on Day 2 of Period 4 will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

For subjects who cannot be contacted before or after discharge in Period 4, and whose reason for discontinuation is not known (eg, withdrew consent or AE, etc.), except those who have completed the trial as defined in Section 3.10 Definition of Completed Subjects, the reason for discontinuation will be classified as "lost to follow-up."

The investigator, subinvestigator, or designee will make 3 documented attempts to contact the subject by telephone. If such attempts fail, the site will attempt to contact the subject via certified mail or an alternative method before assigning a "lost to follow-up" status. For each case of "lost to follow-up," the attempts made to contact the subject, whether or not AEs occurred, date(s) of contact, and contact method will be documented in the CRF.

3.12 Subject Compliance

The subject will be under management of the investigator or subinvestigator during the trial period. The investigator or subinvestigator will instruct the subject to comply with:

- Protocol-specified schedule during trial participation
- The restrictions described in Section 4 Restrictions
- Keeping confidential all the information the subject has acquired through participation in the trial

3.13 Protocol Deviations

In the event of a major deviation from the protocol due to an emergency, accident, or mistake (eg, IMP dispensing error, subject dosing error, concomitant medication error, or violations of other restrictions), the investigator, subinvestigator, or designee will contact the sponsor at the earliest possible time by telephone. The investigator, subinvestigator, medical advisor, and sponsor will come to a joint decision as quickly as possible regarding the subject's continuation in the trial. If the decision reached is to allow the subject to continue in the trial, this must be documented by the investigator or subinvestigator and the sponsor and approved by the medical advisor.

4 Restrictions

4.1 Prohibited Medications

None of the medications specified below, excluding the planned IMP, may be taken for the following periods:

- The use of prescription, over-the-counter or herbal medications, or vitamin supplements is prohibited from 14 days prior to dosing in Period 1 until completion of post-treatment follow-up
- The use of antibiotics is prohibited from 30 days prior to dosing in Period 1 until completion of post-treatment follow-up

4.2 Other Restrictions

4.2.1 Food and Beverages

1) The intake of following food and beverages is prohibited for the duration indicated:

- Products containing St John's wort (*Hypericum perforatum*): Within 14 days prior to Period 1 IMP administration until completion of post-treatment follow-up
- Products containing grapefruit, Seville orange, or star fruit: Within 7 days prior to Period 1 IMP administration until completion of post-treatment follow-up
- Food or beverages containing alcohol: Within 1 day prior to Period 1 IMP administration until completion of post-treatment follow-up
- Food or beverages containing caffeine: Within 1 day prior to IMP administration until discharge in each period
- All food products (ie, fasting): For at least 10 hours before and 4 hours after IMP administration
- Beverages containing sugar: Within 1 day prior to IMP administration until discharge in each period

4.2.2 Smoking, Blood Donation, and Other Activities

The following activities are prohibited between screening examination and completion of post-treatment follow-up:

1) Smoking
2) Blood donation
3) Strenuous exercise

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product which does not necessarily have a causal relationship with the treatment. Adverse events would not include conditions recorded as a concurrent disease at the scheduled screening if such conditions at baseline were fully recognized and did not worsen.

An adverse drug 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 IMP caused the AE.

A 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 or subinvestigator, at immediate risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability.
- Requires hospitalization or prolongation of hospitalization.
  - Hospitalization itself should not be reported as a serious treatment-emergent adverse event (TEAE); whenever possible the reason for 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 serious TEAEs.
- 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.

Immediately Reportable Event (IRE) is:

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4).
- Pregnancies in female partners of male subjects. Although normal pregnancy is not an AE, it must be reported to the sponsor using an IRE form. Pregnancy will only be documented in the CRF as an AE if there is a complication in the mother or abnormality in the newborn.

Clinical Laboratory Value Changes: It is the investigator's or subinvestigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's or subinvestigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator or subinvestigator needs to ascertain if this is an abnormal (ie, clinically relevant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator or subinvestigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered clinically relevant by the investigator or subinvestigator (eg, subject is symptomatic, requiring corrective treatment or further evaluation), leads to treatment discontinuation, or meets one or more of the criteria for being serious, the condition is considered an AE.

Severity: The intensity of an AE will be graded on the following 3-point scale and reported as indicated in the CRF:

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

IMP Causality: Assessment of causal relationship of an AE to the use of IMP:

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

Date of occurrence and resolution (when possible, both date and time of occurrence and resolution)

Date of occurrence: It is the day an AE occurred (or when an AE was first noticed). When a reported AE worsened in severity or seriousness, the date of worsening is recorded as the date of occurrence.

Date of resolution: It is the day an AE resolved (if it is unknown, the day on which it was confirmed that the AE resolved). The date of blood/urine collection is documented as the date of resolution of abnormal laboratory test results. For deaths, the date of death is recorded instead as the date of resolution.

Action taken in relation to IMP administration

Any action taken in relation to IMP administration will be documented as follows:

- Unchanged
- Discontinued
- Interrupted
- Not applicable

Outcome

The outcome of an AE will be recorded by selecting one of the 6 outcomes listed below. For deaths, the date of death is recorded. If the outcome is relieved (recovering), not resolved, or unknown, the date on which the outcome is determined is documented.

- Resolved
- Relieved (recovering)
- Not resolved
- Resolved with sequalae
- Died
- Unknown (eg, unavailable for follow-up for some reason)

5.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will assess subjects for the occurrence of AEs from the time the ICF is signed until the end of the trial. For this trial, information on AEs will be followed until 6 to 8 days after the last dose of IMP in Period 4. To avoid bias in eliciting AEs, subjects should be asked the following nonleading question: "How are you feeling?" All AEs (serious and nonserious) found in the subject must be recorded in the source documents and the CRF provided by the sponsor. AE and serious AE collection is to begin after the subject has signed the ICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as AEs only if there are unusual or severe clinical features that were not present, not experienced earlier, or not expected based on the course of the condition.

When a reported AE worsened in severity or seriousness, the AE should be reported as a new AE in the CRF.

In addition, the sponsor must be notified immediately, normally by e-mail, of any IREs according to the procedure outlined in Section 5.3 Immediately Reportable Events. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator or subinvestigator must report any SAE, potential serious hepatotoxicity, or confirmed pregnancy (in partners of subjects) to the sponsor, normally by e-mail, immediately after the investigator, subinvestigator, or designee becomes aware of the event. An IRE form should then be completed and sent by e-mail to the sponsor, using the contact information on the title page of this protocol. (Please note that the IRE form is a specific form provided by the sponsor and is NOT the AE column in the CRF.)

Subjects experiencing SAEs/IREs should be followed clinically as described in Section 5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events. It is expected that the investigator or subinvestigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥3 times the upper limit of normal (ULN), the total bilirubin level should also be evaluated. If the total bilirubin is ≥2 times the ULN, complete an IRE form with all values listed and also record it as an AE in the CRF.

5.5 Pregnancy

Women of childbearing potential (WOCBP) are women whose menstruation has started and who are not documented as sterile (ie, who have had a bilateral oophorectomy or hysterectomy, or who have been in the menopause for at least 12 months).

For each male subject who is sexually active with WOCBP, there must be a documented agreement that the subject and his partner will take effective measures (ie, 2 different approved methods of birth control) to prevent pregnancy during the course of the trial and for at least 30 days after the last dose of IMP. Unless the subject or his partner is sterile (ie, women who have had a bilateral oophorectomy, have had a hysterectomy, or have been in the menopause for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or agrees to remain abstinent during the trial and for 30 days after the last dose of IMP, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, condom with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive methods will be documented in the CRF. Male subjects must also agree not to donate sperm from trial screening until 30 days have elapsed after the last dose of IMP.

Before enrolling subjects in this clinical trial, the investigator or subinvestigator must review the information below about trial participation as part of the consent obtaining process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, men and WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risks associated with an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risks and the consequences were discussed.

Subjects will be instructed to contact the investigator or subinvestigator immediately if their partners suspect that they might be pregnant (eg, missed or late menstrual cycle) during the trial.

The investigator or subinvestigator must immediately notify the sponsor of any pregnancy in a subject's partner associated with IMP exposure during the trial and until 30 days after the last dose of IMP, and record the event in the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator or subinvestigator to monitor the outcome of the pregnancy.

Protocol-required procedures for follow-up must be performed. Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator or subinvestigator must report to the sponsor, using 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.

5.6 Procedure for Breaking the Blind

In the event of an emergency unblinding (knowledge of a subject’s treatment is required for the subject’s clinical care and safety), the investigator or subinvestigator is to contact the sponsor by phone in order to explain why opening the treatment assignment code is necessary, with both coming to a joint decision if this action is warranted. However, to prevent delays to the investigator, subinvestigator, or medical personnel responding to a potential emergency situation, unblinding of IMP will not be dependent upon the approval from the sponsor (ie, the investigator or subinvestigator will be able to obtain the code breaking information independent of the sponsor). The investigator or subinvestigator must contact the sponsor by telephone or e-mail within 24 hours of opening the code to explain why opening the treatment assignment code was necessary. If the treatment assignment code is unblinded, the sponsor’s Clinical Safety and Pharmacovigilance Department must be notified immediately by the investigator or subinvestigator through the IRE reporting process. Documentation of breaking the blind will be recorded in the subject’s medical record with the date and time the blind was broken, along with the names of the personnel involved, as well as on the appropriate

pages of the CRF for any AEs leading to the breaking of the blind. Once the blind is broken for a subject, that subject is not allowed to reinitiate treatment with IMP.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded in the AE column in the CRF, with the current status (ongoing or resolved/recovered) noted. All nonserious events (excluding IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in the CRF. For any AE that has been identified during the course of the trial, additional relevant medical history information may be requested by the sponsor during data analysis to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation). Follow-up information after the last scheduled contact will be recorded in the subject's medical record.

Based on the results of preceding phase 1 studies, feeling abnormal, feeling hot, erythema, hyperhidrosis, pruritus, rash, urticaria, nausea, epigastric discomfort, and dyspnoea have been selected as AEs of special interest. Because it is suspected that these AEs of special interest will occur, a new formulation with excipients different from those in the previous formulation will be used in this trial. The results of a trial investigating the rate of intravenous administration (263-10-005) also suggest that the AEs of special interest can be decreased by prolonging the duration of administration. However, because the causes of the AEs of special interest are unknown, a prick test will be performed on subjects who experience an AE of special interest in this trial to identify the cause. The investigator, subinvestigator, or designee will perform the prick test after the last dose of IMP (after Period 4 in completed subjects and at an appropriate timing after discontinuation for discontinued subjects) on subjects who experience any AE of special interest during the course of the trial after administration of OPC-61815 at 16 mg, 32 mg, or placebo. The prick test will be performed according to a separately defined procedure. When the investigator or subinvestigator decides that the prick test is unnecessary for a subject experiencing an AE of special interest arising from a clear cause, the reason for the decision will be documented in the source document. The use of anti-histamine drugs is prohibited for 3 days prior to the prick test. Whether a prick test was performed, as well as the date and time, result, and interpretation of the test (if performed), will be documented in the CRF.

5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

In this trial, subjects will be monitored closely for serious AEs and IREs until the end of the trial (last scheduled contact).

Serious AEs and IREs that are identified by or ongoing at the last scheduled contact must be recorded in the AE column in the CRF. If new information related to the SAE or IRE (eg, resolution of the event) was obtained after the last scheduled contact with the subject before the end of the entire trial, the information must be documented in the IRE form and reported to the sponsor and also documented in the AE column in the CRF.

SAEs and IREs must be followed, with any significant follow-up information reported to the sponsor using the IRE form, until the events have resolved or stabilized, or 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 or subinvestigator does not expect any further improvement or worsening of the subject's condition.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring After Last Scheduled Contact

Any new SAEs and IREs that are reported to the investigator or subinvestigator after the last scheduled contact and determined by the investigator or subinvestigator to be related to the use of IMP should be reported to the sponsor. In other words, these events are SAEs and IREs that are identified at the time of follow-up telephone contact or at any other time point after the defined trial period. The investigator or subinvestigator should follow SAEs and IREs identified after the defined trial period and continue to report any significant follow-up information to the sponsor using the IRE form until the events have resolved or stabilized, or the subject is lost to follow-up or has died.

6 Pharmacokinetic/Pharmacodynamic/Pharmacogenomic Analysis

6.1 Pharmacokinetic Analysis Methods

6.1.1 Pharmacokinetic Analysis Set

Pharmacokinetic analysis set includes subjects who are included in the safety analysis set and whose plasma drug concentration was measured.

6.1.2 Pharmacokinetic Analysis

1) Endpoints
   a) Plasma OPC-61815 free form and tolvaptan (OPC-41061) concentrations
   b) PK parameters of plasma OPC-61815 free form and tolvaptan (OPC-41061) C_{max}, AUC_{24h}, AUC_t, AUC_∞, t_{max}, λ_z, AUC_%Extrap, t_{last}, $t_{1/2,z}$, CL^a, CL/BW^a, $V_z{}^a$

      [a]Calculated for OPC-61815 only

2) Statistical analysis method

Descriptive statistics will be calculated in the following manner:

a) Plasma drug concentration
   - At each blood collection time point, descriptive statistics will be calculated by analyte and treatment.
   - Descriptive statistics to be calculated: Number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum.

b) Plasma pharmacokinetic parameters excluding λ_z, λ_z(lower), λ_z(upper), λ_z(point), and λ_z(Rsq)
   - Descriptive statistics will be calculated for each parameter by analyte and treatment.
   - Descriptive statistics to be calculated: Number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum.

6.2 Pharmacodynamic Methods

12-lead Holter ECG parameters will be analyzed at a central ECG laboratory. The central laboratory will obtain 3 snapshots for each scheduled ECG from the 12-lead Holter ECG data sent from the trial site, determine the ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval), and assess waveform patterns. Time windows for data capture are presented in Table 6.2-1. Each data capture will be obtained at an interval of at least 1 minute. The mean from 3 captures will be recorded as the value for each ECG measurement.

Table 6.2-1 Time Windows for 12-lead Holter ECG Data Capture		
Schedule for 12-lead Holter ECG Data Capture[a]		**Time Window**
Day 1	1 hour before IMP administration	Within −5 minutes
	30 minutes before IMP administration	
	15 minutes before IMP administration	
	1 hour after start of IMP administration	Within 5 minutes before end of IMP administration[b]
	1.5 hours after start of IMP administration	Within −5 minutes
	2 hours after start of IMP administration	
	3 hours after start of IMP administration	
	4 hours after start of IMP administration	
	6 hours after start of IMP administration	
	12 hours after start of IMP administration	
Day 2	24 hours after start of Day 1 IMP administration	

[a]: For moxifloxacin, "IMP administration" instead of "start of IMP administration" in the above table

[b]: "Within −5 minutes" for moxifloxacin

6.3 Pharmacokinetic/Pharmacodynamic Methods

For subjects who have QT data and plasma OPC-61815 concentration data after administration of OPC-61815, as well as QT data after placebo administration at the matching time points, differences between OPC-61815 and placebo in change in QTcF interval from baseline at the matching time points are analyzed. A linear mixed-effects model is used, taking plasma OPC-61815 concentration as a fixed effect and subject as a random effect, to investigate the relationships between plasma OPC-61815 concentration and pharmacodynamic parameters.

6.4 Pharmacogenomic Methods

No pharmacogenomic analyses are planned.

7 Statistical Analysis

7.1 Determination of Sample Size

The number of subjects required for central tendency analysis of QTcF, the primary endpoint, was calculated. The number of subjects was calculated to achieve a ≥90% probability of the upper limit of the 2-sided 90% CI (1-sided 95% CI) for the time-matched difference in the mean values for the change in QTcF from baseline between the OPC-61815 and placebo values being lower than 10 msec at all time points after administration of each OPC-61815 dose (16 and 32 mg), and a ≥90% probability of the lower limit of the 2-sided 98% CI (1-sided 99% CI) for the time-matched difference in

the mean values for the change in QTcF from baseline between the moxifloxacin and placebo values being higher than 0 msec in at least one of the 5 assay sensitivity assessment time points (1, 1.5, 2, 3, and 4 hours) after administration of the positive control moxifloxacin. For the assay sensitivity CI, the increase of type 1 error due to the multiplicity of multiple time points was corrected using the Bonferroni method.

Assuming the within-subject standard deviation to be 7.86, the effect size of moxifloxacin (difference between moxifloxacin and placebo in change from baseline) to be 9.6 msec based on the results of a previous trial (Protocol 331-10-242, a clinical trial of brexpiprazole for evaluation of QT/QTc interval in patients with schizophrenia and schizoaffective disorder), the effect size of OPC-61815 to be 3.0 msec (although no data are available) and the individual time points to be independent, the required number of subjects is 45 for each OPC-61815 dose and 21 for moxifloxacin. Estimating a 5% discontinuation rate, a sample size of 48 subjects was considered necessary.

7.2 Analysis Set

The pharmacodynamic analysis set will consist of subjects treated with at least 1 dose of IMP who have QT data at baseline and at least 1 postdose time point.

The safety analysis set will consist of subjects who received at least 1 dose of IMP and have postdose safety data.

7.3 Handling of Missing Data

No data imputation will be performed for missing data.

7.4 Primary and Secondary Endpoint Analyses

12-lead Holter ECG data will be used. For each parameter, the mean of measurements from 3 predose time points (1 hour, 30 minutes, and 15 minutes before IMP administration) in each period will be used as the baseline value. Changes from baseline in corresponding period will be calculated at each postdose time point.

7.4.1 Primary Endpoint Analyses

The primary endpoint is the time-matched difference between the OPC-61815 and placebo data in change from baseline for QTcF in 12-lead Holter ECG. Central tendency analysis for OPC-61815 will be performed for subjects in the pharmacodynamic analysis set who appropriately completed all IMP treatments (OPC-61815 16 mg, OPC-61815 32 mg, placebo, and moxifloxacin) (ie, in whom the administration of the injections was completed within the time windows presented in Section 3.2 Trial Treatments without

interruption after the first 30 minutes) and for whom predose and postdose QT data are available for all 4 treatment periods.

For each OPC-61815 dose (16 mg and 32 mg), the upper limit of the CI for the time-matched difference in the least squares mean for the change in QTcF from baseline compared to the placebo data will be evaluated to determine if it is lower than 10 msec at all postdose time points using the hypothesis presented below. Because the alternative hypothesis is an intersection hypothesis, the 2-sided 90% CI (1-sided 95%) will be calculated without type 1 error adjustment.

$$H_0: \bigcup \{\mu_{A(i)} - \mu_{P(i)} \geq 10\}, \mathrm{i} = 1,2,\cdots,8$$

$$H_1: \bigcap \{\mu_{A(i)} - \mu_{P(i)} < 10\}, \mathrm{i} = 1,2,\cdots,8$$

$\mu_{A(i)}$: Mean change from baseline in QTcF interval at time *i* after OPC-61815 administration

$\mu_{P(i)}$: Mean change from baseline in QTcF interval at time *i* after placebo administration

$\mathrm{i} = 1,2,\cdots,8$ respectively correspond to 1, 1.5, 2, 3, 4, 6, 12, and 24 hours after start of IMP administration

Using a linear mixed effect model with baseline QTcF in each treatment period as a covariate, treatment, sequence, treatment period, time point, and interaction between treatment and time point as fixed effects, and subject as a random effect, point estimates and CIs for the time-matched difference in the least squares mean for the change in QTcF from baseline compared to the placebo data will be calculated.

7.4.2 Secondary Endpoint Analyses

Analyses described in the subsequent sections will be performed per treatment in the pharmacodynamic analysis set.

7.4.2.1 Categorical Analysis

The number and percentage of subjects who fulfilled the following criteria for QTcF interval at least once after IMP administration are calculated. The same calculation will also be performed at each time point.

1) Prolongation of absolute QTc interval:

- QTc interval >450 msec

- QTc interval >480 msec
- QTc interval >500 msec

2) Change from baseline in QTc interval:

- >30 msec increase in QTc interval from baseline
- >60 msec increase in QTc interval from baseline

7.4.2.2 Electrocardiogram (12-lead Holter ECG)

For each parameter, descriptive statistics will be calculated for measurements and changes from baseline at each time point. A shift table of normal/abnormal assessments at each postdose time point compared to baseline will also be created. A frequency distribution of each waveform pattern will be drawn.

7.4.3 Assay Sensitivity Assessment

As an assay sensitivity assessment, moxifloxacin will be evaluated as a positive control using the same analysis set and statistical method as those stated in Section 7.4.1 Primary Endpoint Analyses.

For moxifloxacin, the lower limit of the CI for the time-matched difference in the least squares mean for the change in QTcF from baseline compared to the placebo data will be evaluated if it is higher than 0 msec at any of the postdose time points using the hypothesis presented below. Because of the multiplicity arising from assay sensitivity assessments at 5 postdose time points (1, 1.5, 2, 3, and 4 hours), type 1 error adjustment will be performed using the Bonferroni method, and the 2-sided 98% (1-sided 99%) CI will be calculated.

$$H_0: \bigcap \{\mu_{M(i)} - \mu_{P(i)} \leq 0\}, \mathrm{i} = 1,2,\cdots,5$$

$$H_1: \bigcup \{\mu_{M(i)} - \mu_{P(i)} > 0\}, \mathrm{i} = 1,2,\cdots,5$$

$\mu_{M(i)}$: Mean change from baseline in QTcF interval at time *i* after moxifloxacin administration

$\mu_{P(i)}$: Mean change from baseline in QTcF interval at time *i* after placebo administration

$\mathrm{i} = 1,2,\cdots,5$ respectively correspond to 1, 1.5, 2, 3, and 4 hours after IMP administration

7.5 Analysis of Demographic and Baseline Characteristics

Frequency distribution or descriptive statistics will be calculated for baseline characteristics per sequence and as a whole in the pharmacodynamic analysis set and safety analysis set.

7.6 Safety Analysis

Tabulations discussed in the subsequent sections will be performed per treatment in the safety analysis set.

7.6.1 Adverse Events

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

- TEAEs
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of IMP

When the same AE occurs more than once during one treatment period in the same subject, the most severe event is included in incidence calculation. The incidence of TEAEs potentially causally related to IMP will also be summarized.

In Periods 1, 2, and 3, TEAEs are the events occurring after the start of IMP administration in each period until the start of IMP administration in the subsequent period. In Period 4, AEs that occur after the start of IMP are recorded as TEAEs.

7.6.2 Clinical Laboratory Data

For clinical laboratory data other than qualitative urine tests, descriptive statistics will be calculated for measurements and changes from baseline at each postdose time point. For qualitative urine test data, a shift table comparing test results at each postdose time point to baseline will be created. Each clinical laboratory test result other than qualitative urine tests will be categorized into “within normal,” “below the lower limit of normal,” and “above the upper limit of normal” using the trial site’s reference range to create a shift table of test results at each postdose time point compared to baseline.

7.6.3 Vital Signs and Body Weight

Descriptive statistics will be calculated for measurements and changes from baseline at each postdose time point.

7.6.4 12-lead Electrocardiogram Data

For each parameter, descriptive statistics will be calculated for measurements and changes from baseline at each postdose time point. On normal/abnormal assessment, a shift table comparing data at each postdose time point to baseline will be created.

7.7 Pharmacodynamic Analysis

Discussed in Section 7.4 Primary and Secondary Endpoint Analyses.

8 Management of Investigational Medicinal Product

OPC-61815 16 mg and placebo are test formulations. They are provided for the trial as IMP. Moxifloxacin (Avelox Tablets 400 mg, marketed by Bayer Yakuhin, Ltd.) is provided as the reference formulation. See the Investigator's Brochure of OPC-61815 and/or clinical operations manual for management of IMP and the reference formulation.

8.1 Packaging and Labeling

Both IMP and the reference formulation will be provided to the IMP manager by the sponsor or designated agent. The IMP (OPC-61815 16 mg or placebo) will be provided in vials. Eight vials stored in a box constitute the subject kit. A label stating that the content is for clinical trial use, as well as the protocol number, IMP name, lot number, expiration date, storage conditions, and sponsor's name and address, will be affixed to each vial and box. Moxifloxacin will be provided in the usual commercial box.

8.2 Storage

IMP and the reference formulation will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager who is responsible for IMP preparation at the trial site (non-blinded staff) to prevent any other person from preparing the drugs. The IMP manager must not provide IMP or reference formulation to any subject not participating in the trial.

IMP and the reference formulation will be stored at room temperature.

The clinical site staff will maintain a temperature log in the drug storage area and record the temperature at least once each working day.

8.3 Accountability

The IMP manager must maintain an inventory record of both IMP and the reference formulation received, dispensed, administered, destroyed, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused/partially used IMP and the reference formulation must be returned to the sponsor or a designated agent.

All IMPs and reference formulations returned to the sponsor must be accompanied by appropriate documentation and be clearly identified by the protocol number and trial site number indicated on the outside of the shipping container. Returned supplies should be in the original containers. The assigned trial monitor will facilitate the return of used and partially used IMP and the reference formulation.

8.5 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 IMP and the reference formulation or medical device after it is released for distribution. Examples include, but are not limited to, the following:

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

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator, subinvestigator, or designee must record all PQCs identified through any means during the entire period including the receipt from the sponsor or sponsor’s designee, treatment, destruction, and final check of IMP and the reference formulation.

The investigator, subinvestigator, or designee must notify the sponsor or sponsor's designee of the information specified in Section 8.5.2 Information Required for Reporting Product Quality Complaints by e-mail immediately after becoming aware of the PQC (e-mail address: PQC_263-102-00005@otsuka.jp).

Identification of a PQC by the subject should be reported to the investigator or subinvestigator who should then follow one of the reporting mechanisms below.

Precautions should be taken to maintain blinding at the trial site when reporting a PQC on the quality of the IMP.

8.5.2 Information Required for Reporting Product Quality Complaints

The following information is required for reporting purposes:

- Description of complaint
- Reporter identification (eg, subject, investigator or subinvestigator with site information, non-blinded [responsible for IMP preparation] or blinded staff)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, drug number if assigned)
- Clinical trial protocol information (number and trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process for Product Quality Complaints

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

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.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs concerning the IMP will be handled by the sponsor. PQCs concerning the reference formulation will be assessed/evaluated by the sponsor or, when necessary, discussed with the marketing authorization holder, etc.

9 Records Management

9.1 Source Documents

Source documents are defined as the original records of results of observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data (including drug concentration data, clinical laboratory data, 12-lead ECG analysis reports), screening logs, and recorded data from automated instruments. All source documents pertaining to this trial (excluding 12-lead ECG analysis reports and drug concentration data) will be retained by the trial site and made available for direct inspection by authorized persons.

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

9.2 Data Collection

During each subject's visit to the clinic, the investigator or subinvestigator will record progress notes to document all significant observations and findings. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's or subinvestigator'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 all AEs, and the investigator's or subinvestigator's assessment of relationship to the IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The dated signature (or initials) of all clinicians (or designee) who made an entry in the progress notes.

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. Any changes to information in paper progress notes and other paper source documents will be initialed and dated on the day the change is made by a trial site

staff member authorized to make the change. Changes will be made by striking through the erroneous data with a single line (so as not to obliterate the original data) and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source document by the investigator or subinvestigator. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information in the trial progress notes and other source documents will be entered by trial site personnel directly into the sponsor's electronic data capture (EDC) system. Changes to the data will be captured automatically in the audit trail.

9.3 File Management at the Trial Site

The head of the trial site will ensure that the trial site files are kept in accordance with Section 8 of the ICH Guideline E6 GCP and as required by applicable local regulations. The trial site files will include all source documents, as well as completed CRFs for all subjects screened or enrolled at the trial site. The trial site will take measures to ensure confidentiality and prevent accidental or premature destruction of these documents during the retention period.

9.4 Record Retention at the Trial Site

The trial site will retain all trial-related documents and records for either of the time periods indicated below, whichever is longer. However, if the sponsor requires a longer archiving period, the head of the trial site will consult with the sponsor on the period and procedures for record retention.

- The date 2 years after the manufacturing and marketing approval date. However, if the head of the trial site receives notification from the sponsor that development has been terminated or that the results of the trial will not be submitted with the approval application, the date 3 years after the receipt of such notification; or
- The date 3 years after the termination or completion of the trial.

The trial site must not dispose of any records relevant to this trial without either (1) obtaining written permission from the sponsor or (2) providing the sponsor with an opportunity to collect such records. The trial site will be responsible for retaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. Such documents are open to inspection by the sponsor and relevant regulatory authorities.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to conduct this trial in accordance with established research principles, ICH Guideline E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (ie, to keep the staff updated on the progress of the trial), the sponsor's (or sponsor designee's) monitors will visit the site during the trial, as well as communicate regularly via telephone, e-mail, and written communications. In addition, all investigators, subinvestigators, and trial site clinical personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's (or designee's) Quality Assurance Unit (or its representative) may conduct trial site audits. Audit items will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator is supposed to cooperate with audits.

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

10.3 Protocol Deviations

Due to the complexity of clinical trial protocols and despite training and preventive measures, deviations from the written protocol may occur and potentially result in harm to subjects, biased or inaccurate results, and rejection of all or part of the trial data. Per Section 10.2 of the ICH Guideline E3 Structure and Content of Clinical Study Reports, protocol deviations should be appropriately summarized by site and grouped into different categories such as:

- Those who entered the study even though they did not satisfy the entry criteria.
- Those who developed withdrawal criteria during the study but were not withdrawn.
- Those who received the wrong treatment or incorrect dose.
- Those who received an excluded concomitant treatment.

Otsuka categorizes clinical protocol deviations into major and minor. A major deviation is an intentional or accidental action or omission in a trial conduct that could potentially have a negative impact on the integrity of the trial's primary scientific objectives or has

significant potential to have a negative impact on the safety or efficacy assessments of any trial subject. Major deviations are those that might significantly affect the completeness, accuracy, or reliability of the trial data or that might significantly affect a subject's rights, safety, or well-being.

A minor deviation is an intentional or accidental action or omission during trial conduct in which the protocol is not strictly followed, but which has an inconsequential impact on the integrity of the trial as a whole or the safety or efficacy analyses of an individual subject.

All protocol deviations are to be categorized as major or minor according to the above definitions and only major deviations will be summarized in the clinical study report.

If the same protocol deviation occurs for multiple subjects, it must be recorded separately for each subject.

Investigators or subinvestigators are expected to document potential protocol deviations, as well as their medical assessment regarding the continued participation of the subject(s) due to the protocol deviation, and to record only major deviations in the CRF.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), the Declaration of Helsinki, international ethical principles derived from Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. The trial site will seek approval/favorable opinion by an IRB according to regional requirements and provide that approval/favorable opinion to the sponsor in writing. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling CRFs, the investigator, subinvestigator, and their staff will take adequate measures to protect subject privacy. To this end, a subject number or subject identifier will be used to identify each subject.

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

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly involved in the trial without the sponsor's prior written permission. Subject confidentiality requirements of the country where the trial is conducted will be met. However, authorized regulatory officials and sponsor's authorized

staff members (or representatives) may be allowed full access to inspect and copy the records in accordance with local requirements. All IMPs, subjects' body fluids, and 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 identifiers in CRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials, if necessary, in accordance with local regulations.

13 Amendment Policy

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

When the IRB, investigators, or the sponsor conclude that the protocol amendment substantially alters the trial design 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 is shown by the IRB, written informed consent will be obtained anew from subjects enrolled in the trial before they proceed to continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any publications resulting from the conduct of Otsuka-sponsored trials 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 participants 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 participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

1 Otsuka Pharmaceutical Co., Ltd. Investigator's brochure. OPC-41061, 2017.

2 Otsuka Maryland Research Institute, Inc. Maryland clinical research. A parallel-arm, double-blind, placebo-controlled, multiple dose administration study of tolvaptan oral tablets and moxifloxacin oral tablets on ecg qtc interval in healthy men and women. In-house clinical study report 156-03-245, issued 2005.

3 Oral new quinolone antibacterial agent Avelox Tablets 400 mg (moxifloxacin hydrochloride tablets) [package insert]. Bayer Yakuhin Ltd; Revised Oct 2017.

4 Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare of Japan. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs. PFSB/ELD Notification (1023-1); 2009.

5 Igawa M, Kishi H, Ishibe T. Pathological diagnosis with isoenzyme assay: acid phosphatase (ACP). Jap J Clin Med. 1995;53(5):1203-8.

6 Kato R. Clinical pharmacokinetics. 3rd ed. Tokyo, Japan: Nankodo Co Ltd; 2003:276-80.

7 Takada K. Pharmacokinetics—fundamentals and application—. 2nd ed. Tokyo, Japan: Jiho Inc; 2002:363.

8 International Council for Harmonisation (ICH) [homepage on the Internet]. E6: Good Clinical Practice: Consolidated Guideline [finalized 1996 May, corrected 1996 Jun 1996; cited 2014 Dec 5]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

9 Japan Association of Contract Institutes for Clinical Pharmacology. Standards for intervals during which subjects should refrain from participating in a clinical trial. 2015.

10 New Blood Programme Advisory Committee. Blood withdrawal criteria. 2011.