CLINICAL STUDY PROTOCOL

A Single-center, Open-label, Randomized, 3-Period, 3-Way, Crossover Bioequivalence Study of OPC-41061 Orally Disintegrating Tablets Using 2 Different Formulations and 2 Different Dosing Regimens in Healthy Adult Male Subjects

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

Tolvaptan (OPC-41061)

CLINICAL PROTOCOL

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Protocol No. 156-102-00136

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	1
Sponsor:	Otsuka Pharmaceutical Co., Ltd. 2-9 Kandatsukasa-machi, Chiyoda-ku, Tokyo, 101-8535, Japan
Immediately Reportable Event	Single Case Processing team, Pharmacovigilance Department, Otsuka Pharmaceutical Co., Ltd. 3-2-27 Otedori, Chuo-ku, Osaka-shi, Osaka, 540-0021, Japan e-mail: IRE_156-102-00136@otsuka.jp
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Version No.:	1.0

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Protocol Synopsis

<table>
<tr><td colspan="2">Name of Sponsor: Otsuka Pharmaceutical Co., Ltd.
Name of Investigational Medicinal Product: Tolvaptan (OPC-41061)</td><td>Protocol No.: 156-102-00136</td></tr>
<tr><td>Trial Title:</td><td colspan="2">A Single-center, Open-label, Randomized, 3-Period, 3-Way, Crossover Bioequivalence Study of OPC-41061 Orally Disintegrating (OD) Tablets Using 2 Different Formulations and 2 Dosing Regimens in Healthy Adult Male Subjects</td></tr>
<tr><td>Trial Objectives:</td><td colspan="2">To assess the bioequivalence of OPC-41061 OD tablets and OPC-41061 conventional tablets at 15 and 30 mg in healthy adult male subjects</td></tr>
<tr><td>Phase of Development:</td><td colspan="2">Phase: 1
Type of trial: Bioequivalence study</td></tr>
<tr><td>Trial Design:</td><td colspan="2">A single-center, open-label, randomized, 3-period, 3-way, crossover study using 2 formulations in 2 dosing regimens, will be conducted in 2 cohorts.

[Cohort 1]
<table>
<tr><th>Dose</th><th>Group</th><th>Period 1</th><th>Period 2</th><th>Period 3</th></tr>
<tr><td rowspan="3">15 mg</td><td>Conventional tablet first</td><td>Conventional tablet</td><td>OD tablet without water</td><td>OD tablet with water</td></tr>
<tr><td>OD tablet with water first</td><td>OD tablet with water</td><td>Conventional tablet</td><td>OD tablet without water</td></tr>
<tr><td>OD tablet without water first</td><td>OD tablet without water</td><td>OD tablet with water</td><td>Conventional tablet</td></tr>
</table>
[Cohort 2]
<table>
<tr><th>Dose</th><th>Group</th><th>Period 1</th><th>Period 2</th><th>Period 3</th></tr>
<tr><td rowspan="3">30 mg</td><td>Conventional tablet first</td><td>Conventional tablet</td><td>OD tablet without water</td><td>OD tablet with water</td></tr>
<tr><td>OD tablet with water first</td><td>OD tablet with water</td><td>Conventional tablet</td><td>OD tablet without water</td></tr>
<tr><td>OD tablet without water first</td><td>OD tablet without water</td><td>OD tablet with water</td><td>Conventional tablet</td></tr>
</table>
A washout period of 72 hours will be set from postdose in Period 1 until predose in Period 2 and from postdose in Period 2 until predose in Period 3. This study consists of a main study and an add-on subject study in additional subjects.</td></tr>
<tr><td>Subject Population:</td><td colspan="2">A total of 84 healthy adult male subjects at least 20 years and less than 40 years of age will be enrolled.</td></tr>
</table>

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Inclusion/Exclusion Criteria:	Inclusion Criteria: 1) Japanese males at least 20 years and less than 40 years of age at the time of informed consent 2) Body weight of at least 50.0 kg 3) BMI [body weight in kg / (height in m)^2] of at least 17.6 kg/m^2 and less than 25.0 kg/m^2 4) Judged by the investigator or subinvestigator to be capable of providing written informed consent prior to the start of any trial-related procedures and capable of complying with the trial procedures for this study. Main Exclusion Criteria: 1) Judged by the investigator, subinvestigator, or sponsor to have a clinically significant abnormality in results of the screening examination (including a notable deviation from the site's standard values) or a medical history that could place the subject at risk or affect the evaluation of drug absorption, distribution, metabolism, or excretion 2) History of alcohol or drug dependence or abuse within 2 years prior to the trial 3) History or current symptoms of hepatitis or acquired immunodeficiency syndrome (AIDS) or positive test results for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV), or judged to have syphilis based on the results of Treponema pallidum (TP) antibody test or rapid plasma reagin (RPR) test 4) History of any severe drug allergy 5) Positive results in alcohol screening test or urine drug screening test at time of screening examination or trial site admission 6) Use of any other investigational medicinal product (IMP) within 120 days prior to Period 1 IMP administration 7) Consumption of any food or beverage containing St. John's wort within 14 days prior to Period 1 IMP administration 8) Consumption of any food or beverage containing grapefruit, Seville orange, or star fruit within 7 days prior to Period 1 IMP administration 9) Judgment by the investigator or subinvestigator that the subject should not participate in the study for any other reason

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Trial Site: Soseikai Medical Group Fukuoka Mirai Hospital

Investigational Medicinal Product, Dose and Regimen, Treatment Period, Formulation, and Route of Administration:

[Test drug: Tolvaptan OD tablet]

Cohort	Dose (mg)	Active Ingredient (Content per tablet)	Dose per Administration	Dosing Regimen (Single oral administration in a fasting state)
1	15	Tolvaptan 15 mg	1 tablet	With water: Administered with approx. 150 mL of water.
2	30	Tolvaptan 30 mg		Without water: Tablet disintegrated on the tongue and swallowed immediately with saliva

[Comparator: Tolvaptan conventional tablet]

Cohort	Dose (mg)	Active Ingredient (Content per tablet)	Dose per Administration	Dosing Regimen (Single oral administration in a fasting state)
1	15	Tolvaptan 15 mg	1 tablet	Administered with approx. 150 mL of water.
2	30	Tolvaptan 30 mg		

Duration of treatment: Single administration a total of 3 times on 3 separate days

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Variables:	[Bioequivalence] 1) Primary variables: AUC_t and C_{max} of tolvaptan 2) Reference variables: • Plasma concentration-time profile of tolvaptan • AUC_∞, MRT_∞, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, and t_{last} of tolvaptan • By-subject ratios of AUC_t, C_{max}, AUC_∞, MRT_∞, and λ_z of tolvaptan for administration of OD tablet with and without water to those for administration of conventional tablet • Difference (value for OD tablet minus value for conventional tablet) in t_{max} by subject between administration of OD tablet without water and administration of conventional tablet and between administration of OD tablet with water and administration of conventional tablet [Safety Variables] Body weight, vital signs (body temperature, blood pressure, and pulse rate), clinical laboratory tests, 12-lead electrocardiography (ECG), physical examination, and adverse events
Statistical Methods:	For the AUC_t and C_{max} of tolvaptan, data will be log-transformed and analysis of variance (ANOVA) will be performed using group (group receiving conventional tablet first, group receiving OD tablet without water first, and group receiving tolvaptan OD tablet with water first), formulation, dosing regimen, subjects within group, and administration period (Period 1, Period 2, and Period 3) as factors. For the AUC_t and C_{max} of tolvaptan, the 90% confidence interval (CI) of the ratio of the geometric mean values for the 2 formulations (OD tablet without water vs conventional tablet and value for OD tablet with water vs conventional tablet) will be calculated. If evaluable data cannot be obtained for a subject for all periods (1, 2, and 3), sensitivity analysis will be performed including such subjects.
Scheduled Duration of the Trial:	Duration of the trial: Dec 2016 to Dec 2017 Scheduled duration of individual subjects' participation: Maximum of 37 days (3 to 29 days for screening period and 8 days for treatment period)

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
AUC_t	Area under the concentration-time curve from time zero to the last observable concentration at time t
AUC_%Extrap	Percentage of AUC due to extrapolation from t_{last} to infinity $[(AUC_{\infty} - AUC_t) / AUC_{\infty} \times 100]$
BMI	Body mass index
BUN	Blood urea nitrogen
CIOMS	Council for International Organizations of Medical Science
CL/F	Apparent clearance of drug from plasma after extravascular administration
CL/F/BW	CL/F normalized in body weight
C_{max}	Maximum (peak) plasma concentration
CPK	Creatine phosphokinase
DILI	Drug Induced Liver Injury
EDC	Electronic data capture
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional review board
IRE	Immediately reportable event
LDH	Lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{∞}	Mean residence time from time zero to infinity
OD	Orally disintegrating
PQC	Product quality complaint
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
$t_{1/2,z}$	Terminal-phase elimination half-life
TEAE	Treatment-emergent adverse event
t_{last}	Time of last measurable [positive] concentration
t_{max}	Time to maximum [peak] plasma concentration
λ_z	Apparent terminal-phase disposition rate constant (first-order)

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1 Introduction

Tolvaptan is a nonpeptide, cyclic adenosine monophosphate (cAMP)-dependent, arginine vasopressin (AVP) V_2 receptor antagonist synthesized by Otsuka Pharmaceutical Co., Ltd. Tolvaptan increases water excretion (water diuresis) without affecting electrolyte excretion by inhibiting water reabsorption at the renal collecting ducts. The compound was granted marketing approval in Japan on 27 Oct 2010 under the trade name of "Samsca® tablets 15 mg" for the treatment of "volume overload in heart failure when an adequate response is not obtained with other diuretics (eg, loop diuretics)." Subsequently, tolvaptan was granted additional indications for the "treatment of body fluid retention in hepatic cirrhosis when an adequate response is not obtained with other diuretics (eg, loop diuretics)" on 13 Sep 2013 and "Suppression of progression of autosomal dominant polycystic kidney disease (ADPKD) in patients with increased kidney volume and a rapid rate of increase" on 24 Mar 2014 and is currently in the reexamination period. Samsca tablets 7.5 mg and tablets 30 mg were respectively approved on 04 Feb 2013 and 24 Mar 2014.

In the United States, the drug acquired marketing authorization for "hypervolemic and euvolemic hyponatremia in patients with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH) on 19 May 2009. In Europe, it was approved for the "treatment of adult patients with hyponatremia secondary to SIADH" on 03 Aug 2009. Tolvaptan has now been approved in over 40 countries though for different indications.

Samsca tablets are used in the clinical setting in patients covering a wide age range and with different disorders, including those with relatively severe heart failure in whom an adequate response is not obtained with other diuretics. Only the tablet formulations of tolvaptan are available, but other dosage forms that are easier for the patients to use should be added to the lineup for better medication adherence. In particular, swallowing tablets can be problematic in elderly patients with swallowing difficulties. Clinicians desire an orally-disintegrating (OD) tablet formulation so that such patients can use the drug without water. This study has been planned in order to develop an OD tablet formulation to add to the currently available non-OD tablet for increased treatment options and also for better adherence.

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1.1 Nonclinical Data

Tolvaptan OD tablet 15 mg showed a similar dissolution profile to the tolvaptan conventional tablet 15 mg in solution with a pH of 6.8, the pH level typically found in the small intestine where the drug is absorbed (2nd fluid for dissolution test of the Japanese Pharmacopoeia).

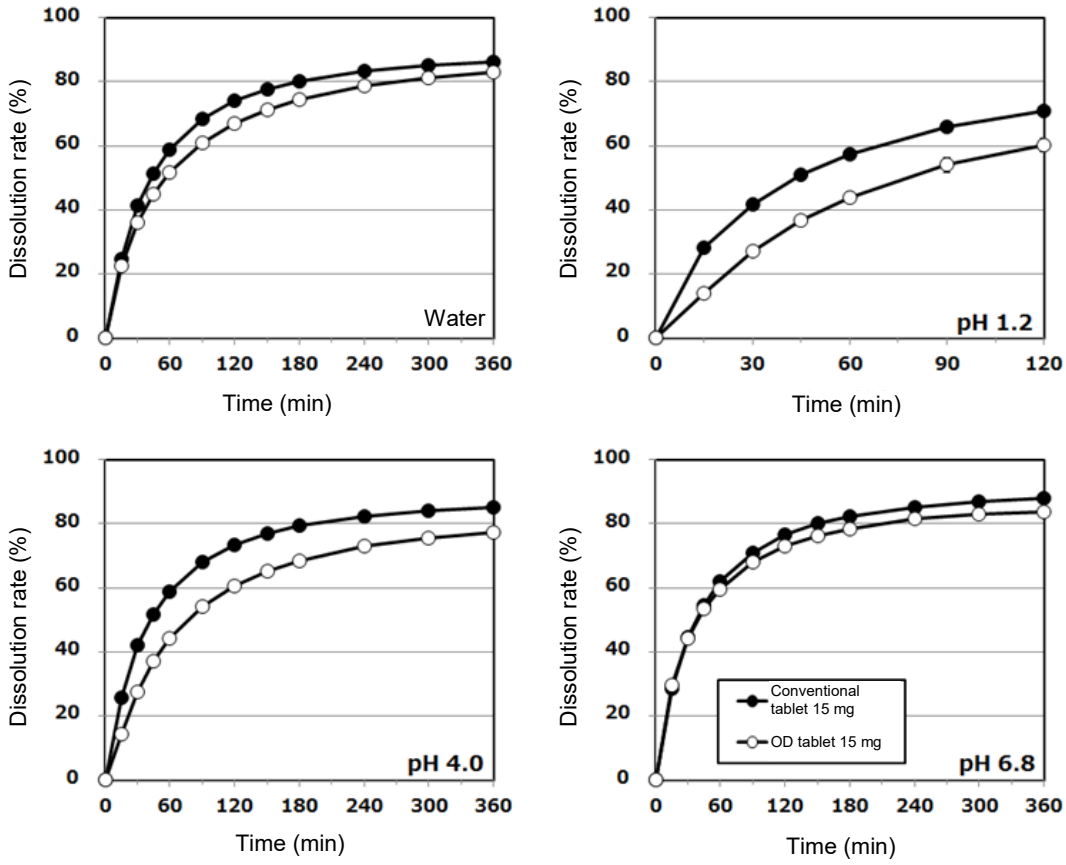

Figure 1.1-1 **Dissolution Profile of Tolvaptan Conventional Tablet 15 mg and Tolvaptan OD Tablet 15 mg. Volume of Dissolution Medium, 900 mL; Test Method, Paddle Method at 50 rpm (Number of Vessels, 3; Mean ± Standard Deviation)**
pH 1.2: JP 1st Fluid for Dissolution Test,
pH 4.0: Diluted McIlvaine's Buffer,
pH 6.8: JP 2nd Fluid for Dissolution Test

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Tolvaptan OD tablet 30 mg showed a similar dissolution profile to the tolvaptan conventional tablet 30 mg in a solution with a pH of 6.8, the pH level typically found in the small intestine where the drug is absorbed (2nd fluid for dissolution test of the Japanese Pharmacopoeia).

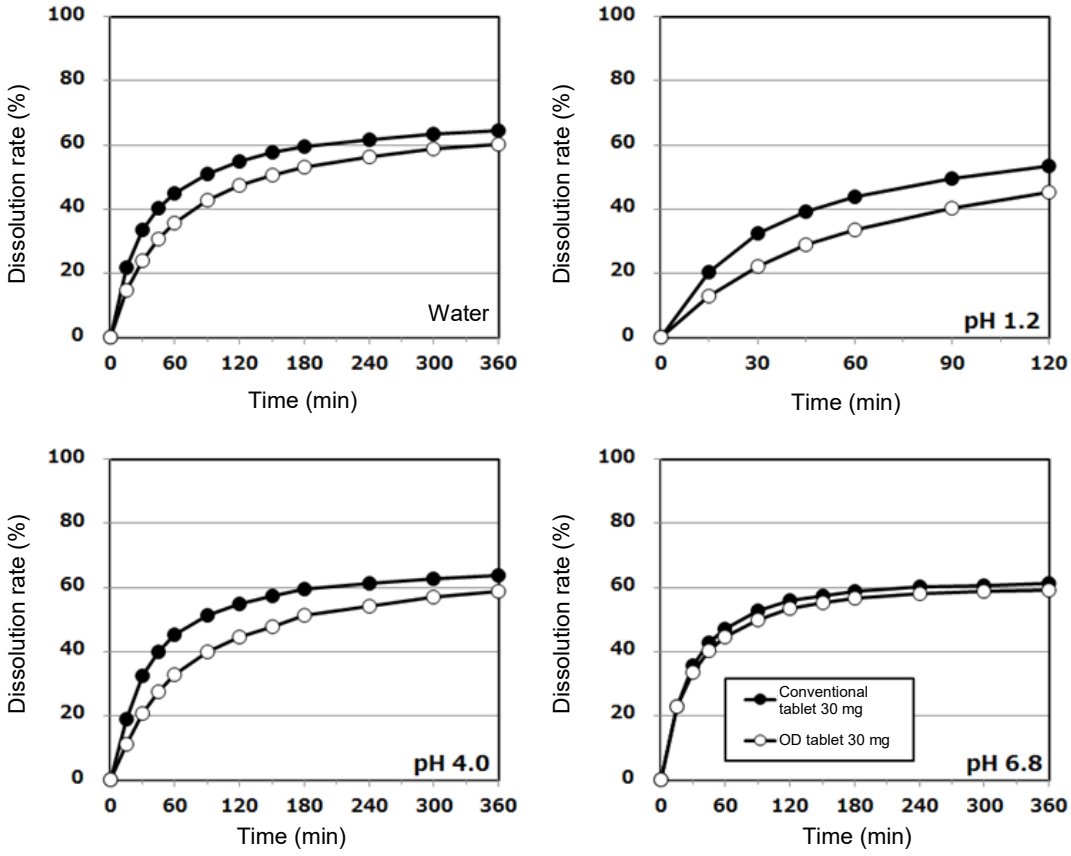

Figure 1.1-2 **Dissolution Profile of Tolvaptan Conventional Tablet 30 mg and Tolvaptan OD Tablet 30 mg. Volume of Dissolution Medium, 900 mL; Test Method, Paddle Method at 50 rpm (Number of Vessels, 3; Mean ± Standard Deviation)**
pH 1.2: JP 1st Fluid for Dissolution Test,
pH 4.0: Diluted McIlvaine's Buffer,
pH 6.8: JP 2nd Fluid for Dissolution Test

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1.2 Clinical Data

No prior clinical study has been conducted using the same tolvaptan OD tablet as that to be used in this study. The results of a single-dose study conducted in 2001 using the conventional tablets 15 mg and 30 mg (156-00-001) are discussed below.

1.2.1 Single Oral Dose Study (156-00-001)

OPC-41061 15 to 120 mg was administered once orally to 40 healthy adult male volunteers under fasted conditions.

1) Pharmacokinetic Results

- Plasma pharmacokinetics of OPC-41061 after dosing of 15 to 120 mg showed large inter-individual variability. DM-4103 showed the highest plasma concentration (C_{max} and AUC_t) and is therefore considered the primary metabolite of OPC-41061. Among OPC-41061 metabolites, MOP-21826 was consistently below the lower limit of quantitation throughout the study period in all subjects (treated with 60 mg or 90 mg).
- The AUC_t and C_{max} of OPC-41061 showed a fairly dose-dependent increase without obvious nonlinear changes as the dose increased (15 to 120 mg). Statistical evaluation confirmed dose proportionality (linearity) in AUC_t but not in C_{max}. The $t_{1/2,z}$ of OPC-41061 was prolonged as the dose increased. The mean $t_{1/2,z}$ in the 120 mg group was about 3 times that in the 15 mg group (9.33 hours vs 3.33 hours).
- The cumulative urinary excretion of OPC-41061 had mostly reached plateau by 48 hours postdose in all subjects. The $fe_{,48h}$ of OPC-41061 was less than 1% in all subjects, indicating urine excretion does not account much for elimination of OPC-41061 from the system. Among metabolites, urinary concentrations of DM-4103, DM-4105, and MOP-21826 were consistently below the lower limit of quantitation in all subjects treated with 60 mg or 90 mg.

2) Pharmacological Results

- Twenty-four-hour cumulative urine volume dose-dependently increased, and, in the highest dose (120 mg) group, it reached 11945.8 mL, approximately 4.6 times that in the placebo group. The urine excretion rate until 8 hours postdose (urine was pooled in 2-hour periods until 8 hours postdose) increased to approximately 700 to 800 mL/h (in 60 to 120 mg groups). It subsequently decreased, but diuretic effects were observed until 24 hours postdose in the 60 to 120 mg groups.
- No marked increase or dose-dependent change was observed in 24-hour cumulative urine sodium excretion. Twenty-four-hour cumulative urine potassium excretion increased with dose.
- Urine osmolality decreased from immediately after dosing (from the interval of 0 to 2 hours postdose) accompanied by hypotonic urine and a high positive value for free water clearance from immediately after dosing. These water diuretic effects lasted longer at higher dose levels.

- Plasma AVP concentration increased after dosing and remained high at 24 hours postdose. Serum sodium concentration increased after dosing but remained within normal physiological limits. No notable change was observed in serum potassium concentration.
- Fluid balance showed a negative value in the interval of 0 to 2 hours in a dose-dependent manner but showed gains from Day 2.

3) Safety Results

- The incidence of adverse events in the study was 50.0% (21/42 subjects) in the OPC-41061 groups and 14.3% (2/14 subjects) in the placebo group. The incidence of adverse events at least possibly related to the investigational medicinal products (= adverse drug reactions [ADRs]) was 45.2% (19/42 subjects) and 7.1% (1/14 subjects), respectively.
- By dose, the incidence of adverse events (in the descending order) was 100% (6/6 subjects) in the 120 mg and 90 mg groups, 41.7% (5/12 subjects) in the 30 mg group, and 33.3% (2/6 subjects) in the 15 mg, 45 mg, and placebo groups. No adverse event was reported in the 60 mg group.
- Frequent adverse events (≥ 5% incidence) in the OPC-41061 groups were "thirst" (8 subjects), "nasopharyngitis" (4 subjects), and "blood osmolarity increased," "blood uric acid increased," and "headache NOS" (3 subjects each).
- Serious adverse events ("sinus arrest" and "bradycardia NOS") occurred in 1 subject in the 30 mg group. A causal relationship between these events and OPC-41061 could not be ruled out, but both events resolved without intervention.
- On laboratory values, no clinically significant variations were seen in any group including the placebo group.
- On vital signs (blood pressure, pulse rate, and body temperature), no clinically significant changes were seen excluding the serious adverse events reported in the 30 mg group. Body weight decreased after dosing in all groups. The decrease was larger in the OPC-41061 groups than in the placebo group. The mean decrease in 24 hours after dosing was 1.42 to 2.20 kg in the OPC-41061 groups and 0.89 kg in the placebo group.
- On electrocardiogram (ECG) findings, 1 subject in the 30 mg group experienced serious adverse events ("sinus arrest" and "bradycardia NOS"). Two subjects in the 90 mg group also had tachycardia (mild). These changes were judged to be "abnormal." However, they were transient changes and resolved without intervention.

1.3 Known and Potential Risks and Benefits

In patients with body fluid retention in heart failure, ADRs including laboratory test abnormalities were reported in 143 out of 213 subjects (67.1%) included in the safety dataset of a clinical study conducted in Japan. Common ADRs were thirst (65 events or 30.5%), blood urea nitrogen increased (28 events or 13.1%), and blood uric acid increased (20 events or 9.4%) among others (at the time of approval).

In patients with body fluid retention in hepatic cirrhosis, ADRs including laboratory test abnormalities were reported in 162 out of 266 subjects (60.9%) included in the safety dataset of a clinical study conducted in Japan. Common ADRs were thirst (83 events or 31.2%) and pollakiuria (45 events or 16.9%) among others (at the time of approval of the new indication).

In patients with ADPKD, ADRs including laboratory test abnormalities were reported in 851 (including 117 Japanese) (88.6%) out of 961 (including 118 Japanese) subjects included in the safety dataset of a global study. Common ADRs were thirst (677 events or 70.4%), pollakiuria (503 events or 52.3%), polyuria (366 events or 38.1%), headache (135 events or 14.0%), and polydipsia (100 events or 10.4%) among others (at the time of approval of the new indication).

Refer to the latest Investigator's Brochure (IB) for more information about the adverse events reported after treatment with tolvaptan in clinical studies.

Tolvaptan has been granted multiple indications and is administered to patients with multiple diseases covering a wide age range. The development of an OD tablet formulation to add to the conventional tablet will increase treatment options for patients and should improve patient adherence.

2 Trial Rationale and Objectives

2.1 Trial Rationale

The same administration route, indications, and dose and regimen as those for Samsca tablets are expected to be granted for the tolvaptan OD tablet to be used in this study. In other words, the new OD tablet will be filed under the category "1-(8) new dosage form of a drug under reexamination" and for the purpose of demonstrating bioequivalence with Samsca tablets. With reference to the Guidelines for Bioequivalence Studies of Generic Products[1] and the 2000 Guidebook for Approval Application for Pharmaceutical Products,[2] a "bioequivalence study comparing (the conventional tablet administered with water) with (the proposed formulation administered without water)" and another "bioequivalence study comparing (the conventional tablet administered with water) with (the proposed formulation administered with water)" were planned.

This randomized, 3-period 3-way crossover study using 2 different formulations and 2 different dosing regimens has therefore been designed to evaluate the plasma pharmacokinetics and bioequivalence of the OD tablet (with water), OD tablet (without water), and conventional tablet administered once orally to Japanese healthy adult male subjects.

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This protocol has been written generally in accordance with the Guidelines for Bioequivalence Studies of Generic Products. [1] The intended doses for this study (30 mg, 15 mg) are within the approved dose range. The selected safety endpoints and their evaluation time points have also been selected after due consideration. This study will be conducted using hospitalized subjects so that any medical emergencies can be dealt with properly should they occur. The above arrangements and considerations are considered adequate for the ethical and scientific conduct of this study.

2.2 Dosing Rationale

2.2.1 Regimens

The 2000 Guidebook for Approval Application for Pharmaceutical Products[2] states "For the application for approval of a new OD tablet following the approval of a conventional tablet formulation, a 'bioequivalence study comparing (the conventional tablet administered with water) with (the proposed formulation administered without water)' and another 'bioequivalence study comparing (the conventional tablet administered with water) with (the proposed formulation administered with water)' are in principle recommended to characterize the OD tablet." This is the reason for the intended regimens with and without water. The Guidelines for Bioequivalence Studies of Generic Products[1] stipulate "In principle, drugs are given to subjects with 100 to 200 mL water (normally 150 mL) after fasting for more than 10 hours." This is the rationale for the selected volume (about 150 mL) of water to be used for administration with water.

2.2.2 Dose Levels

Producing the marketed tolvaptan formulation (conventional tablet) and OD tablet in the same tablet size necessarily results in different compositions between the tolvaptan OD tablets 15 mg and 30 mg. Because of this, this study evaluates bioequivalence at each dose level (namely, separate comparisons between the tolvaptan OD tablet 15 mg and tolvaptan conventional tablet 15 mg and between the tolvaptan OD tablet 30 mg and tolvaptan conventional tablet 30 mg).

2.3 Trial Objectives

To assess the bioequivalence of OPC-41061 OD tablets and OPC-41061 conventional tablets at 15 and 30 mg in healthy adult male subjects.

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3 Trial Design

3.1 Type/Design of Trial

This single-center, open-label, randomized, 3-period 3-way, crossover study using 2 different formulations and 2 different dosing regimens investigates bioequivalence between tolvaptan OD and conventional tablets in 84 healthy adult male subjects in 2 cohorts. Bioequivalence between the OD and conventional 15 mg tablets will be investigated in Cohort 1. In Cohort 2, bioequivalence between the OD and conventional 30 mg tablets will be investigated.

The trial design schematic is presented in Figure 3.1-1 (applicable to both cohorts).

This study consists of a main study and an add-on subject study in additional subjects for both Cohort 1 and 2. With reference to the Guidelines for Bioequivalence Studies of Generic Products, [1] the add-on subject study will be conducted only once when bioequivalence is not demonstrated in the main study for the reason specified in Section 7.7, Decision on Whether to Conduct an Add-on Subject Study. Both the main study and add-on subject study will be conducted in the same manner with the exception of sample size. When bioequivalence is demonstrated in only one of the cohorts, the add-on subject study will be conducted in the cohort in which bioequivalence was not demonstrated.

Subjects will be admitted to the trial site the day before dosing in Period 1. Subjects will be discharged, after blood collection for safety and pharmacokinetic evaluations, following the end of treatment examination in Period 3.

Subjects will be randomly assigned to the conventional tablet first group, OD tablet with water first group, or OD tablet without water first group according to the randomization code and receive either the 15 mg conventional tablet or OD tablet in Cohort 1 and either the 30 mg conventional tablet or OD tablet in Cohort 2.

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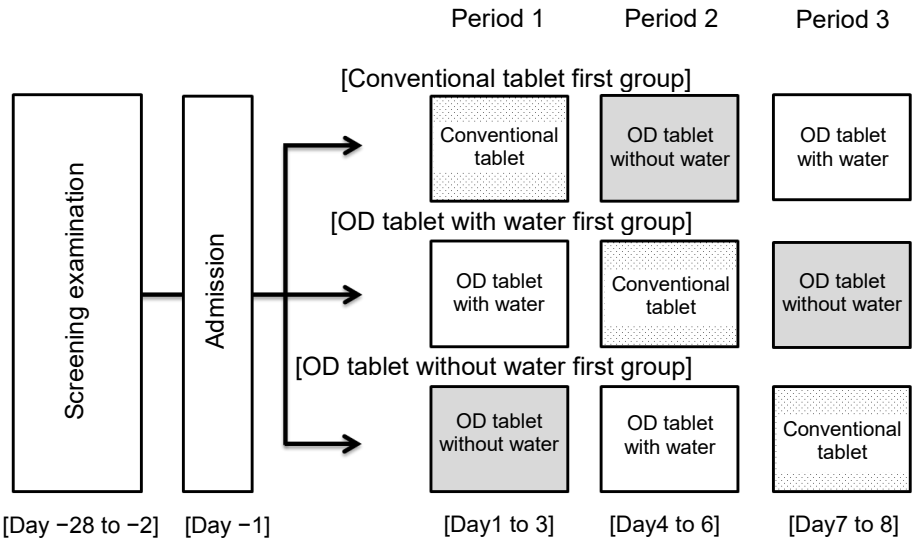

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

3.2.1 Investigational Medicinal Products

3.2.1.1 Tolvaptan OD Tablet

1) Administered with water
   One tolvaptan OD tablet 15 mg or 30 mg will be administered with about 150 mL of water under fasting conditions. Investigational medicinal products (IMPs) will be administered after at least 10 hours of fasting. Subjects will not be allowed to eat until 4 hours postdose. Fluid intake will not be allowed from 2 hours before to 2 hours after dosing, excluding water given to swallow the tablet.

2) Administered without water
   The subject will disintegrate one tolvaptan OD tablet 15 mg or 30 mg in the mouth (on the tongue) under fasting conditions and promptly swallow with saliva. Both formulations will be administered after at least 10 hours of fasting. Subjects will not be allowed to eat until 4 hours postdose. Fluid intake will not be allowed from 2 hours before to 2 hours after dosing.

3.2.1.2 Tolvaptan Conventional Tablet

One tolvaptan conventional tablet 15 mg or 30 mg will be administered with about 150 mL of water under fasting conditions.

Both formulations will be administered after at least 10 hours of fasting. Subjects will not be allowed to eat until 4 hours postdose. Fluid intake will not be allowed from 2 hours before to 2 hours after dosing, excluding water given to swallow the tablet.

3.2.2 Treatment Period

After single oral dosing in Period 1, there is a 72-hour washout period, followed by single oral dosing in Period 2 (different from the formulation + regimen combination in Period 1). After single oral dosing in Period 2, there is a 72-hour washout period, followed by single oral dosing in Period 3 (different from the formulation + regimen combination in Periods 1 and 2).

[Rationale for treatment period and washout period]
Treatment period: according to the statement in the Guidelines for Bioequivalence Studies of Generic Products, [1] "In principle, bioequivalence studies should have a single-dose design."

Washout period:
In the single oral dose study (156-00-001), food effect study (156-00-002), and single-dose part of the oral repeated-dose study (156-00-003) conducted in Japan, the mean elimination half-life of tolvaptan after administration of 30 mg was 3.89, 4.39 (in a fasting state), and 3.33 hours, respectively. Guidelines for Bioequivalence Studies of Generic Products[1] state "Washout periods should usually be more than 5 times the elimination half-life of the unchanged active ingredient or active metabolites to be measured." The longest reported elimination half-life in these studies was 8.5 hours (Study 156-00-002, Subject No. 001-0016). At least 5 times 8.5 hours means the washout period should be at least 43 hours. Plasma tolvaptan concentration at 48 hours postdose was below the lower limit of quantitation (5 ng/mL) in all subjects enrolled in the above 3 studies. Because 2 ng/mL is being adopted as the lower limit of quantitation in the present study, 72 hours is selected for washout to ensure plasma tolvaptan concentration decreases to sufficiently low levels between doses to ensure accurate bioequivalence evaluation.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

A total of 84 healthy adult male subjects at least 20 years and less than 40 years of age will be enrolled.

Any enrolled subject who withdraws consent or is judged not to be able to receive IMP before the start of IMP administration will be replaced with a reserve subject.

Neither subject enrollment nor replacement will take place for subjects who are withdrawn from the trial after randomization.

3.3.2 Subject Selection and Numbering

A subject identifier comprising a 3-digit trial site number, the letter "S," and 5-digit serial number per trial site will be assigned to each subject (eg, "101S00001").

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be freely obtained from all subjects. Consent will be documented on a written informed consent form (ICF). The ICF will be approved by the same institutional review board (IRB) that approves this protocol.

Each ICF will comply with the ICH (International Conference on Harmonisation) Good Clinical Practice (GCP) Guideline[3] and local regulatory requirements.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

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

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

Subjects may be asked to sign additional ICFs if the protocol is amended to significantly add or change procedures.

3.4.2 Inclusion Criteria

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

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Table 3.4.2-1 Inclusion Criteria	
1.	Japanese males at least 20 years and less than 40 years of age at the time of informed consent
2.	Body weight of at least 50.0 kg
3.	BMI [body weight in kg / (height in m)^2] of at least 17.6 kg/m^2 and less than 25.0 kg/m^2
4.	Judged by the investigator or subinvestigator to be capable of providing written informed consent prior to the start of any trial-related procedures and capable of complying with the trial procedures for this study.

[Rationale for inclusion criteria]

1 The lower age limit is set so that only adults are enrolled. The upper limit of 40 is selected because the risk of other complicating diseases increases with age and also because older individuals may have reduced metabolic capacity. Only males are to be enrolled because males do not become pregnant or menstruate, both of which may affect study procedures.
2 This criterion is to ensure appropriate pharmacokinetic and safety evaluations.
3 This criterion is to restrict inter-individual variability due to obesity in pharmacokinetics in subjects.
4 This criterion is for ethical considerations.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria	
1.	Judged by the investigator, subinvestigator, or sponsor to have a clinically significant abnormality in results of the screening examination (including a notable deviation from the site's standard values) or a medical history that could place the subject at risk or affect the evaluation of drug absorption, distribution, metabolism, or excretion. Examples include, but are not limited to, a history or current medical conditions related to the heart, liver, kidneys, nervous system, stomach and intestines, respiratory organs, blood, or immune system.
2.	History of alcohol or drug dependence or abuse within 2 years prior to the trial
3.	History or current symptoms of hepatitis or acquired immunodeficiency syndrome (AIDS) or positive test results for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV), or judged to have syphilis based on the results of Treponema pallidum (TP) antibody test or rapid plasma reagin (RPR) test
4.	History of any severe drug allergy
5.	Positive results in alcohol screening test or urine drug screening test at time of screening examination
6.	Prior experience of blood collection difficulties
7.	Use of any other IMP within 120 days prior to Period 1 IMP administration
8.	Blood collection (eg, donation) of > 200 mL within 30 days, > 400 mL within 90 days, or 1200 mL within 1 year prior to Period 1 IMP administration
9.	Consumption of any food or beverage containing St. John's wort within 14 days prior to Period 1 IMP administration
10.	Consumption of any food or beverage containing grapefruit, Seville orange, or star fruit within 7 days prior to Period 1 IMP administration
11.	Use of any prescribed drug, over-the-counter (OTC) drug, Chinese herbal medicine, or vitamin supplement within 14 days prior to Period 1 IMP administration
12.	Use of tobacco products within 60 days prior to Period 1 IMP administration, or positive urine cotinine test at screening.

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Table 3.4.3-1 Exclusion Criteria	
13.	Occupational exposure to insecticides or organic solvents within 30 days prior to the trial
14.	A blood pressure measurement after at least 3 minutes of rest that deviates from the institutional reference range
15.	A pulse rate measurement after at least 3 minutes of rest that deviates from the institutional reference range
16.	History of severe bleeding or bleeding tendency
17.	Sexually active males who are not capable of or do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, or condom with spermicide.
18.	History of serious mental disorders
19.	Seeing or is scheduled to see a doctor at another hospital or clinical department during the trial
20.	Judgment by the investigator or subinvestigator that the subject should not participate in the study for any other reason

[Rationale for exclusion criteria]	
1 to 6	These criteria are set as safety precautions.
7	This criterion is set to define a period during which participation in a clinical study is generally inappropriate.
8	This criterion is set based on the standards for blood donation established by the New Blood Program Advisory Committee.
9 to 13	These criteria are set to prevent unintended effects on pharmacokinetics.
14 to 20	These criteria are for safety precautions.

Re-entry of individuals judged to be ineligible based on the screening examination is not allowed. If the investigator or subinvestigator decides to perform a retest (eg, clinical laboratory test), the retest must be documented in accordance with the trial site's procedure.

3.5 Variables

3.5.1 Bioequivalence

3.5.1.1 Primary Variable

AUC_t and C_{max} of tolvaptan

3.5.1.2 Reference Variables

1) Plasma concentration-time profile of tolvaptan
2) AUC_∞, MRT_∞, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, and t_{last} of tolvaptan
3) By-subject ratios of AUC_t, C_{max}, AUC_∞, MRT_∞, and λ_z of tolvaptan for administration of OD tablet with and without water to those for administration of conventional tablet
4) Difference (value for OD tablet minus value for conventional tablet) in t_{max} by subject between administration of OD tablet without water and administration of

conventional tablet and between administration of OD tablet with water and administration of conventional tablet

3.5.2 Safety

Body weight, vital signs (body temperature, blood pressure, and pulse rate), clinical laboratory tests, 12-lead ECG, physical examination, and adverse events

3.6 Measures to Minimize/Avoid Bias

The sponsor will prepare the randomization code. Subjects are randomized to 3 groups in each cohort according to the randomization code.

No bias will occur, even without blinding, because AUC_t and C_{max} values based on plasma drug concentration will be used for evaluation in this study. This is the reason for selecting the open-label design.

3.7 Trial Procedures

Trial procedures and assessment time points are summarized in Figure 3.7-1 and Table 3.7-1, respectively (same across the cohorts).

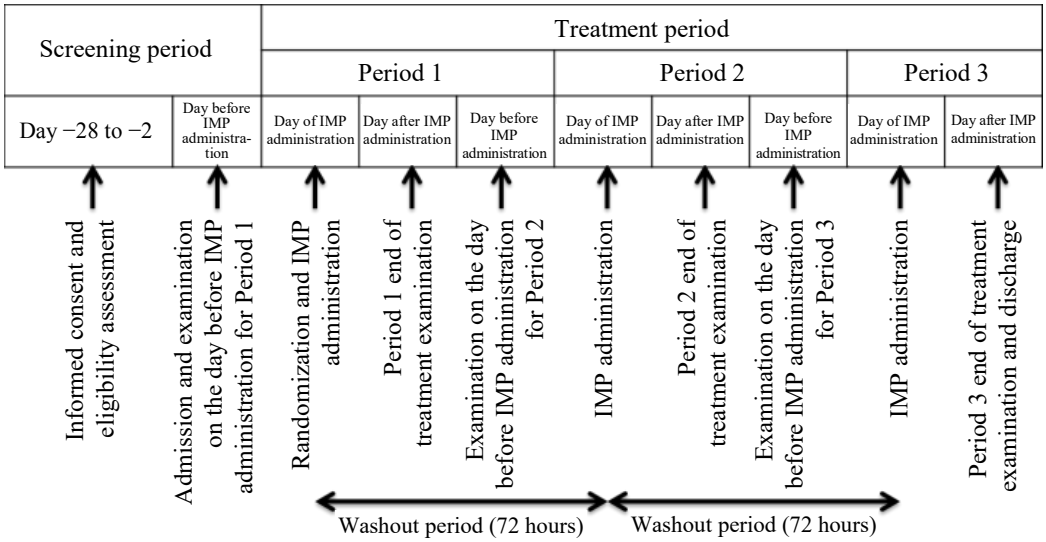

Figure 3.7-1 Trial Procedures

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Table 3.7-1 Schedule of Assessments

	Day −28 to −2	Day −1, 3, and 6	Day 1, 4, and 7											Day 2, 5, and 8		At Discon-tinuation
			Predose	0 h	1 h	2 h	3 h	4 h	5 h	6 h	8 h	10 h	12 h	16 h	24 h	
Informed consent	○															
Subject demographics	○															
Eligibility assessment	○															
IMP administration				○												
Height/Body weight	○[a]		○												○	○
Blood collection for plasma concentration measurement			○		○	○	○	○	○	○	○	○	○	○		
Physical examination	○	○	○												○	○
Vital signs	○	○	○			○									○	○
Clinical laboratory test	○		○												○	○
Immunological test	○															
Urine alcohol, drug, cotinine tests	○															
12-lead ECG	○		○												○	○
Randomization			○[c]													
Adverse events	←															→
Concomitant medications/therapy	←															→
Admission/Discharge	Visit	Admission[b]													Discharge[d]	

a: Height is measured only from Day −28 to −2.
b: Only on Day −1 (Subjects will continue to be hospitalized on Day 3 and 6 from Day −1.)
c: Only on Day 1
d: The subject will be discharged only on Day 8, not on Day 2 or 5.

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3.7.1 Schedule of Assessments (Both Cohorts)

3.7.1.1 Screening

After informed consent, the subject will undergo the examinations and tests specified below within 28 days prior to IMP administration in Period 1 (between Day −28 and −2) for eligibility assessment. Enrolled subjects and reserve subjects will be selected from qualified subjects. Test results (with the eligibility assessment) will be documented in medical records together with the reason for an "ineligible" assessment.

Tests and Examinations	Time Point(s) and Acceptable Time Window
Height, body weight, BMI (weight will be measured in a fasting state) Height will be measured to 0.1 cm. BMI will be calculated (to one decimal place) from the height and body weight measured at screening using the equation below. Equation: BMI = Body weight (kg) / {Height (m)}^{2}	Between 28 and 2 days before IMP administration in Period 1
Subject demographics (Birth date, sex, race, ethnicity, medical history, current symptoms, drinking habit, smoking habit)	
Physical examination	
Vital signs (body temperature, blood pressure, pulse rate)	
Clinical laboratory test (blood and urine collection)	
Immunological test (HBsAg, HCV antibody, HIV antigen/antibody, TP antibody, and RPR test)	
Urine alcohol, drug, and cotinine tests	
12-lead ECG	
Adverse events	
Concomitant medications/therapy and restricted foods specified in Restrictions after informed consent	

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

Each enrolled subject and reserve subject will visit the trial site in the afternoon the day before IMP administration in Period 1 (Day −1) and be asked to reconfirm his consent. Subsequently, he will undergo the observations, tests, and examinations listed below for eligibility assessment and be admitted when judged to be eligible. The subject will have dinner at around 1900 and fast from 2200.

Tests and Examinations	Time Point(s) and Acceptable Time Window
Physical examination	As appropriate
Vital signs (body temperature, blood pressure, pulse rate)	
Adverse events	
Concomitant medications/therapy and restricted foods specified in Restrictions	

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3.7.1.3 Day Before IMP Administration in Periods 2 and 3 (Day 3 and 6)

Subjects who have completed the preceding Period will be enrolled in next Period. In the morning the day before IMP administration (Day 3 or 6), each subject will undergo the same observations, tests, and examinations as those on Day −1 for eligibility assessment. The subject will have dinner at around 1900 and fast from 2200.

3.7.1.4 Day of IMP Administration (Day 1, 4, and 7)

3.7.1.4.1 Before IMP Administration

The subject will undergo the observations, tests, and examinations listed below.

Tests and Examinations	Time Point(s) and Acceptable Time Window
Body weight	Within 3 hours before IMP administration
Physical examination	
Vital signs (body temperature, blood pressure, pulse rate)	
Blood collection for plasma drug concentration measurement (before dosing on the day of IMP administration)	
Clinical laboratory test (blood and urine collection)	
12-lead ECG	
Adverse events	
Concomitant medications/therapy and restricted foods specified in Prohibited Medications	

3.7.1.4.2 Subject Enrollment and Treatment Assignment (Only on Day 1)

Subjects will be randomized per cohort. Enrolled subjects will be randomly assigned to the conventional tablet first group, OD tablet with water first group, or OD tablet without water first group according to the randomization code, in ascending order of subject identifier.

3.7.1.4.3 Subject Replacement (Only on Day 1)

Each enrolled subject who withdraws consent or is judged not to be able to receive IMP before the start of IMP administration will be replaced with a reserve subject.

Neither subject enrollment nor replacement will take place for discontinued subjects after IMP administration.

3.7.1.4.4 IMP Administration

The subject will receive the IMP once orally at about 0900 and swallow with about 150 mL of water or saliva (without water). The exact time of administration in individual subjects should be adjusted for subsequently scheduled blood collection and tests. The IMP will be administered after at least 10 hours of fasting. Fluid intake will not be

allowed from 2 hours before to 2 hours after dosing. Except for that period, subjects will be allowed to intake fluids freely. Eating will not be allowed for 4 hours after dosing.

3.7.1.4.5 After IMP Administration

Subjects who did not receive the IMP will be discharged from the trial site.

Subjects who remain at the site will undergo the observations, tests, and examinations listed below. They will receive lunch at about 1300 and dinner at about 1900.

Tests and Examinations	Time Point(s) (hours after dosing)	Acceptable Time Window
Blood collection for plasma concentration measurement	1, 2, 3, 4, 5, 6, 8, 10, 12	±5 minutes
Vital signs (body temperature, blood pressure, pulse rate)	2	±30 minutes
Adverse events	As appropriate	–
Concomitant medications/therapy and restricted foods specified in Prohibited Medications	As appropriate	–

3.7.1.5 Day After IMP Administration (Day 2, 5, and 8)

Subjects will undergo the observations, tests, and examinations listed below.

Observations, Tests, and Examinations	Time Point(s) (hours after dosing)	Acceptable Time Window
Blood collection for plasma concentration measurement	16	±5 minutes
Body weight	24	Within 60 minutes after the scheduled time (after awakening)
Physical examination	24	±60 minutes
Vital signs (body temperature, blood pressure, pulse rate)	24	±60 minutes
Clinical laboratory test (blood and urine collection)	24	±60 minutes (urine may be collected from immediately after awakening)
12-lead ECG	24	±60 minutes
Adverse events	As appropriate	–
Concomitant medications/therapy and restricted foods specified in Prohibited Medications	As appropriate	–

3.7.1.6 At Discontinuation

Each subject who is withdrawn from the trial after IMP administration in Period 1 will undergo the observations, tests, and examinations shown in the table below. No all of the

procedures are to be mandatory if not feasible (eg, when the subject refuses to undergo the procedures specified for discontinuation or there is a medical emergency affecting the subject at that time). Also, the same procedures the subject has undergone on the day of trial discontinuation may be omitted.

Observations, Tests, and Examinations	Time Point(s) and Acceptable Time Window
Body weight	At discontinuation
Physical examination	
Vital signs (body temperature, blood pressure, pulse rate)	
Clinical laboratory test (blood and urine collection)	
12-lead ECG	
Adverse events	
Concomitant medications/therapy and restricted foods specified in Restrictions	

3.7.1.7 Follow-up Examination

Subjects with adverse events unresolved at the end-of-trial examination or at the time of withdrawal will be followed up according to Section 5.7, Follow-up of Adverse Events.

3.7.2 Safety Assessments

3.7.2.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.2.2 Clinical Laboratory Assessments

The clinical laboratory data specified in Table 3.7.2.2-1 will be collected at scheduled time points. The date and time of each blood and urine collection will be recorded in source documents and in the case report form (CRF).

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Table 3.7.2.2-1 Clinical Laboratory Assessments

Hematology Red blood cell (RBC) count White blood cell (WBC) count WBC count with differentials (neutrophil, lymphocyte, monocyte, basophil, eosinophil) Platelet count Hemoglobin Hematocrit	**Serum Chemistry:** Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT) Alkaline Phosphatase (ALP) Lactic Dehydrogenase (LDH) Gamma Glutamyl Transferase (GGT) Protein, total Albumin Bilirubin, total Cholesterol, total Triglycerides Glucose Blood urea nitrogen (BUN) Creatinine Uric acid Creatine phosphokinase (CPK) Serum electrolytes (sodium, potassium, chloride, calcium)
Urinalysis Blood Glucose pH Protein Specific gravity Sediments Bilirubin Urobilinogen Ketone body	

3.7.2.3 Physical Examination and Vital Signs (Body Temperature, Blood Pressure, Pulse Rate)

3.7.2.3.1 Physical Examination

The subject is to undergo an examination at the scheduled time points and physical findings are to be recorded. The head, ears, eyes, nose and pharynx, chest, abdomen, urogenital organs, limbs, nervous system, and skin and mucosa are examined individually. The investigator or subinvestigator will be responsible for evaluating physical findings. Whenever possible, physical examinations in each subject will be performed by the same clinician.

The date and time of examination and observed physical findings will be documented in source documents and the CRF.

When clinically significant physical findings not seen at the baseline examination are observed after IMP administration, they will be documented as adverse events and followed up until a stable outcome is achieved.

3.7.2.3.2 Vital Signs (Body Temperature, Blood Pressure, Pulse Rate)

Vital signs will be measured at scheduled time points.

1) Body temperature

Axillary temperature will be measured in tenths of a degree Celsius and documented together with the date and time of measurement in source documents and the CRF.

2) Blood pressure (diastolic and systolic), pulse rate

Blood pressure and pulse rate will be measured after the subject has rested in the sitting position for at least 3 minutes and documented together with the date and time of measurement in source documents and the CRF.

3.7.2.4 Electrocardiogram Assessments

A 12-lead electrocardiogram will be obtained at scheduled time points after the subject has rested in the supine position for at least 5 minutes. Heart rate, RR interval, PR interval, QRS interval, QT interval, and corrected QT interval (Fridericia's correction, QTcF; Bazett's formula, QTcB) will be measured. The investigator or subinvestigator will evaluate the ECG data and documents them together with the date and time of measurement, normal/abnormal assessment, and other findings in source documents and the CRF.

3.7.2.5 Body Weight

The subject's body weight will be measured to 0.1 kg at scheduled time points. The body weight value will be documented together with the date and time of measurement in source documents and the CRF.

3.7.3 Pharmacokinetic Assessments

3.7.3.1 Time Points

Cohort 1 and 2: Before IMP administration and 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 hours postdose in each period

[Rationale for blood collection time points]

A single oral dose study (156-00-001), food effect study (156-00-002), oral repeated-dose study (156-00-003), and food effect study using the finished product (156-07-002) have been completed in Japan. In these studies, the mean t_{max} and mean elimination half-life were 2.18 to 3.21 hours and 3.33 to 4.39 hours, respectively, after dosing of 15 mg and 30 mg tablets. The studies also reported the linearity of tolvaptan pharmacokinetics (excluding C_{max}) in the dose range of 5 to 480 mg, [4] suggesting a similar half-life for the 15 mg and 30 mg tablets. The time period at least 3 times the sum of t_{max} + elimination half-life, calculated based on the data from the above 4 studies (as recommended for calculation of a biological fluid sampling time point in the Guidelines for Bioequivalence Studies of Generic Products[1]) was not less than 16 hours. Based on the above, the 11 time points (immediately before dosing, 4 points around the t_{max} [1, 2, 3, and 4 hours postdose], and 6 points in the elimination phase [5, 6, 8, 10, 12, and 16 hours postdose]

were selected for each period with reference to the Guidelines for Bioequivalence Studies of Generic Products. [1]

3.7.3.2 Blood Collection Procedure and Sample Treatment

About 4 mL of blood will be drawn each time from a vein and collected in a sodium heparin tube. The date and time of each blood collection will be recorded in source documents and the CRF.

After collection, the tube will be gently inverted a few times and placed in ice water. Then the sample will be immediately (within 45 minutes after collection) centrifuged at about 4°C and about 1710 × G for about 10 minutes. The separated plasma will be divided into 2 polypropylene sample tubes in nearly equal volumes and frozen at −15°C or lower within about 90 minutes after separation. A sample label on which essential information (protocol number, subject identifier, time of sampling, etc.) is entered at the trial site will be affixed to each plasma sample tube.

3.7.3.3 Transportation

Plasma samples will be kept frozen with dry ice and sent to the bioanalytical laboratory. Two samples obtained at one time point from one subject will be sent in separate shipments to the bioanalytical laboratory.

3.7.3.4 Plasma Drug Concentration Measurement

Plasma tolvaptan concentration will be determined at the bioanalytical laboratory according to the validated procedure at the laboratory.

3.7.3.5 Reporting of Measurement Results

The bioanalytical laboratory will retain the source documents of plasma drug concentration measurements. The sponsor will keep the copy of electronic file of plasma drug concentration measurements submitted by the bioanalytical laboratory.

3.7.3.6 Handling of Remaining Samples

The bioanalytical laboratory will keep remaining samples frozen and dispose of them after completion of the clinical study report.

3.7.4 End of Trial

The end of trial date is defined as the day on which the last subject completes the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

If the sponsor terminates or suspends the trial for safety or any other unexpected 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

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and GCP. The head of the trial site will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After IMP administration, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject or may become medically necessary due to adverse events (AEs), required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. The discontinued subject should be encouraged to undergo the examinations specified for discontinuation.

3.8.3.2 Documenting Reasons for Treatment Discontinuation

All subjects have the right to withdraw their consent from further participation in the trial at any time. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. The subject's participation in the trial must be terminated when any of the following applies:

- Reasons related to AE:
  - Subject decides to discontinue because of annoyance or discomfort due to a non-serious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - Serious adverse event (SAE)
    - Other potentially IMP-related safety concerns or AEs
- Death
- Reasons unrelated to medical condition (provide detail and review AE history with subject)

- Withdrawal of informed consent (complete written withdrawal of consent form)
- Lost to follow-up
- Termination of all or part of the trial by the sponsor

If the subject (temporarily interrupts or) discontinues IMP due to an AE, the investigator will follow the event until it has resolved or stabilized according to Section 5.7, Follow-up of Adverse Events.

3.8.3.3 Withdrawal of Consent

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

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

A subject who withdraws consent should be encouraged to undergo the examinations specified for discontinuation.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on treatment.

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

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which the subject is evaluated for primary and/or reference objectives of the trial irrespective of whether or not the subject received all doses of the IMP. Subjects who undergo the last scheduled evaluation during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete the evaluation in Period 3 will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted after discharge in Period 3 will be classified as "lost to follow-up."

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

3.12 Subject Compliance

The subject should be under the supervision of the investigator during the trial. The investigator will guide the subject so that the subject complies with the restrictions specified in Section 4, Restrictions.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

If the subject uses any drug other than the IMP between the time of consent and the end of treatment examination in Period 3 or discontinuation, the name, purpose of use, regimen, dose, route, and start and end dates (and time if possible) will be documented in source documents and the CRF. If the subject undergoes any non-drug therapy during the same period, its name, purpose, and start and stop dates will be also documented in source documents.

When the subject needs a prohibited drug or therapy to eliminate immediate hazards to the subjects (eg, for the treatment of AEs), the subject is to terminate the trial according to Section 3.8.3, Individual Subject Discontinuation.

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Prohibited medication/therapy	Restricted period
Any prescription and OTC drug other than the IMP	Between 14 days before IMP administration in Period 1 and discharge in Period 3
Any non-drug therapy	During hospitalization

4.2 Other Restrictions

4.2.1 Subject Admission

The subject will be hospitalized between the day before IMP administration in Period 1 and the day after IMP administration in Period 3 (8 nights and 9 days).

4.2.2 Self Care

The subject will be instructed to avoid strenuous exercises, excessive eating and drinking, and irregular hours such as staying up late during participation in the trial.

4.2.3 Restricted Foods

- The table below specifies the food products not allowed to be taken by subjects, together with the applicable periods of restriction.

Food	Restricted period
Any food/beverage containing methylxanthine	During hospitalization
Any food/beverage containing alcohol	Between 3 days before IMP administration in Period 1 and discharge in Period 3
Any food/beverage containing St. John's wort	Between 14 days before IMP administration in Period 1 and discharge in Period 3
Any food/beverage containing grapefruit, Seville orange, or star fruit	Between 7 days before IMP administration in Period 1 and discharge in Period 3
Smoking	Between 60 days before IMP administration in Period 1 and discharge in Period 3

- The subject will be allowed to take only permitted foods/beverages during hospitalization.
- During hospital stay, the subject will have breakfast (not served on the day of IMP administration), lunch, and dinner at about 0900, 1300, and 1900, respectively, each day. The same foods/beverages will be served to all subjects. When a scheduled test/blood collection conflicts with a meal, the subject will undergo the test/blood collection first.
- Eating will not be allowed between 10 hours before and 4 hours after IMP administration in each period.
- Fluid intake will not be allowed from 2 hours before to 2 hours after IMP administration in each period. Except for that period, subjects will be allowed to intake fluids freely.
- For each clinical laboratory test (excluding the tests scheduled the same day as IMP administration), eating will not be allowed from 2200 the day before to blood/urine collection.

4.2.4 Prohibition of the Supine Position

The subject will not be allowed to assume the supine position, excluding when it is necessary for an observation/test/examination, for at least 4 hours after IMP administration.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as a symptom at screening for pre planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

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

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- 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 adverse events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential Drug Induced Liver Injury (DILI) case (see Section 5.4).
- Pregnancies in partners of male subjects are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE CRF if there is an abnormality or symptom.

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

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

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

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

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

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and CRFs provided by the sponsor. Serious AE collection is to begin after a subject has signed the ICF and end at the time of discharge.

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 an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

A reported AE that undergoes a change in severity, seriousness, or toxicity should be reported as a new AE on the CRF.

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

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, AE related to occupational exposure, DILI, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail to the sponsor. (Please note that the IRE form is NOT the AE CRF.)

Subjects experiencing SAEs should be followed clinically until the events are resolved, stabilized, or the subject is lost to follow-up. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Drug-Induced Liver Injury

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), a total bilirubin level should also be evaluated. If the total bilirubin is ≥2 times the ULN, complete an IRE form with all values listed and also report as an AE on the CRF.

5.5 Pregnancy

Women of child-bearing potential (WOCBP) are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months).

For men who are sexually active with partners of child-bearing potential, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, or condom with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

During the trial, all subjects should be instructed to contact the investigator immediately if they suspect their partners might be pregnant (eg, missed or late menstrual cycle).

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

The investigator must report to the sponsor, on appropriate 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

Not applicable.

5.7 Follow-up of Adverse Events

For this trial, information on AEs will be followed up until discharge in Period 3.

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE CRF with the current status noted. If a subject has an AE or has not recovered from an AE at the last scheduled contact, follow-up contacts will be scheduled at least every

4 weeks until the event is resolved, stabilized, or the subject is lost to follow-up. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing on the CRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation). The follow-up information after the last scheduled contact will be recorded in the subject's medical record.

5.7.2 Follow-up of Serious Adverse Events

This trial requires that subjects be actively monitored for SAEs up to discharge in Period 3.

Serious AEs that are **identified or ongoing at the last scheduled contact** must be recorded on the AE CRF page and reported to the sponsor according to the reporting procedures outlined in Section 5.3. All SAEs that are ongoing at the last scheduled contact will be recorded as ongoing on the CRF.

This may include **unresolved previously reported SAEs, or new SAEs.** The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up. The investigator will continue to report any significant follow-up information to the sponsor until the event is resolved, stabilized, or the subject is lost to follow-up with the IRE form.

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

Any new SAEs reported by the subject to the investigator that occur **after the last scheduled contact**, and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow SAEs identified after the last scheduled contact until the events are resolved, stabilized, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor until the event is resolved, stabilized, or the subject is lost to follow-up with the IRE form.

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6 Pharmacokinetic/pharmacodynamic Analysis

6.1 Pharmacokinetic Analysis

6.1.1 Primary Variables

AUC_t and C_{max} of tolvaptan

6.1.2 Reference Variables

1) Plasma concentration-time profile of tolvaptan
2) AUC_∞, MRT_∞, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, and t_{last} of tolvaptan
3) By-subject ratios of AUC_t, C_{max}, AUC_∞, MRT_∞, and λ_z of tolvaptan for administration of OD tablet with and without water to those for administration of conventional tablet
4) Difference (value for OD tablet minus value for conventional tablet) in t_{max} by subject between administration of OD tablet without water and administration of conventional tablet and between administration of OD tablet with water and administration of conventional tablet

6.1.3 Datasets for Analysis

The datasets for analysis are the same as that specified in Section 7.2.2, Bioequivalence Analysis Set.

6.1.4 Calculations of PK Parameters

1) AUC_t, C_{max}, AUC_∞, MRT_∞, tmax, λ_z, AUC_%Extrap, $t_{1/2,z}$, t_{last}, and CL/F are to be calculated per subject by non-compartmental analysis.
2) Actual time after each IMP administration will be used in the calculations.
3) The value 0 will be imputed for each plasma drug concentration measurement below the lower limit of quantitation in the calculations of PK parameters and descriptive statistics. For calculation of λ_z from each blood sampling time point after t_{max}, a measurement below the lower limit of quantitation will be treated as missing.
4) CL/F/BW is to be calculated by dividing CL/F by body weight (kg) before IMP administration in each period.
5) The ratio between the formulations and regimens is to be calculated per parameter in each subject by [Value after dosing of OD tablet without water] / [Value after dosing of conventional tablet] and [Value after dosing of OD tablet with water] / [Value after dosing of conventional tablet] (parameters, AUC_t, C_{max}, AUC_∞, MRT_∞, and λ_z).

6) Differences in t_{max} ([t_{max} after dosing of OD tablet without water] − [t_{max} after dosing of conventional tablet] and also [t_{max} after dosing of OD tablet with water] − [t_{max} after dosing of conventional tablet]) are to be calculated per subject.

6.1.5 Calculation of Descriptive Statistics

Descriptive statistics of the parameter specified in 1) of Section 6.1.2 are to be calculated per blood sampling time point by cohort and regimen (conventional tablet, OD tablet without water, and OD tablet with water). For each parameter listed in 2) of Section 6.1.2, descriptive statistics are to be calculated by cohort and regimen (conventional tablet, OD tablet without water, and OD tablet with water).

6.2 Pharmacodynamic Analysis

No pharmacodynamic analysis is planned.

7 Statistical Analysis

7.1 Sample Size

With reference to the Guidelines for Bioequivalence Studies of Generic Products, [1] the sample size for this study was calculated as the number of subjects required to demonstrate that the 90% confidence intervals of the geometric mean ratios of the AUC_t and C_{max} of tolvaptan (OD tablet without water vs conventional tablet and OD tablet with water vs conventional tablet) fall inside the bioequivalence range of ln(0.8) to ln(1.25).

Of the prior crossover studies of tolvaptan in healthy adults, Study 156-00-002 reported the largest intra-individual variability (AUC_t and C_{max}, 0.033 and 0.056, respectively). Sample size calculation was performed using the method proposed by Diletti, et al. (1991) [5] based on the C_{max}, in which intra-individual variability was large.

When the ratio of the expected C_{max} with the tolvaptan OD tablet (administered with or without water) to that with the tolvaptan conventional tablet is assumed to be 1.05, at least 12 subjects per group are required to achieve a power of at least 90%. To account for withdrawals and dropouts, the sample size for this study was set to 14 subjects per group for 1 cohort, for a total of 42 subjects.

7.2 Datasets for Analysis

7.2.1 Safety Analysis Set

The safety analysis set will include all subjects that were administered at least one dose of IMP.

7.2.2 Bioequivalence Analysis Set

The bioequivalence analysis set will include all subjects with both AUC_t and C_{max} values across Period 1, 2, and 3.

7.3 Handling of Missing Data

Missing values will not be imputed.

7.4 Primary and Reference Endpoint Variables

The following analyses will be performed for the bioequivalence analysis set per cohort.

7.4.1 Primary Variable Analysis

1) For the AUC_t and C_{max} of tolvaptan, data will be log-transformed and analysis of variance (ANOVA) will be performed using group (group receiving conventional tablet first, group receiving OD tablet without water first, and group receiving tolvaptan OD tablet with water first), formulation and dosing regimen, subjects within group, and administration period (Period 1, Period 2, and Period 3) as factors. The analysis will use natural logarithms.
2) For the AUC_t and C_{max} of tolvaptan, the 90% confidence intervals (CIs) of the ratio of the geometric mean values for the 2 formulations (OD tablet without water vs conventional tablet and OD tablet with water vs conventional tablet) will be calculated. Bioequivalence between the formulations and between the dosing regimens is to be demonstrated when the 90% confidence intervals fall inside the range of ln(0.8) to ln(1.25). Bioequivalence between the OD tablet and conventional tablet is to be established when the bioequivalence criteria are met between the OD tablet administered without water and conventional tablet and also between the OD tablet administered with water and conventional tablet. When an add-on subject study is conducted, bioequivalence is to be assessed in the same manner using the pooled data of both the main study and add-on subject study.
3) When there are subjects without evaluable parameters across Periods 1, 2, and 3, sensitivity analysis including those subjects will be performed.

7.4.2 Reference Variable Analyses

For the AUC_∞, MRT_∞, t_{max}, and λ_z of tolvaptan, data (excluding t_{max}) will be log-transformed and analysis of variance (ANOVA) will be performed using group (group receiving conventional tablet first, group receiving OD tablet without water first, and group receiving tolvaptan OD tablet with water first), formulation and dosing regimen, subjects within group, and administration period (Period 1, Period 2, and Period 3) as factors. The analysis will use natural logarithms. The effects of the formulation and dosing regimen will be analyzed at a significance level of 5%.

7.5 Analysis of Demographic and Baseline Characteristics

The distribution (or descriptive statistics) of the age, height, body weight (at screening), BMI, and medical history or current symptoms of the bioequivalence analysis set (per group and entire analysis set) will be calculated in each cohort. If necessary, the same calculation will be performed for other analysis sets.

7.6 Safety Analysis

Analysis will be performed by formulation and dosing regimen in each safety analysis set per cohort. Values obtained immediately before IMP administration in each period will be handled as baseline.

7.6.1 Adverse Events

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

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

7.6.2 Clinical Laboratory Data

For each laboratory parameter (excluding qualitative urine tests), descriptive statistics of measurements and changes from baseline at each time point will be calculated. For qualitative urine tests, a shift table comparing results to baseline by time point will be created. For each laboratory parameter other than qualitative urine tests, a shift table summarizing the test results at each time point classified into “within normal” “below the lower limit of normal,” or “above the upper limit of normal” (using the institutional reference ranges) with comparison to baseline will be created.

7.6.3 Physical Examination and Vital Signs

For each physical examination parameter, a shift table summarizing the findings at each time point compared to baseline will be created.

For each vital sign parameter, descriptive statistics of measurements and changes from baseline at each time point will be calculated.

7.6.4 Electrocardiogram Data

For each 12-lead ECG parameter, descriptive statistics of measurements and changes from baseline at each time point will be calculated. A shift table of ECG findings at each time point compared to baseline assessments will be created. Categorical analysis of corrected QT intervals (QTcF and QTcB) and their changes from baseline at each time point will be performed to calculate the number and percentage of subjects.

7.7 Decision on Whether to Conduct an Add-on Subject Study

When bioequivalence is not demonstrated due to insufficient samples in the main study, an add-on subject study in additional subjects may be conducted once in accordance with the procedures of the main study. When bioequivalence is demonstrated in only one of the cohorts, an add-on subject study will be conducted in the cohort in which bioequivalence is not demonstrated.

The add-on subject study must enroll at least half the number of subjects enrolled in the main study. An add-on subject study will not be conducted when:

1) When the point estimates of the differences in mean log-transformed AUC_t and C_{max} between the conventional tablet and OD tablet do not fall inside the range of ln(0.8) to ln(1.25) in the main study; or
2) The sample size calculated from the results of the main study for the add-on subject study is ethically inappropriate and/or not scientifically feasible.

When data from the add-on subject study are pooled with those of the main study for analysis, the study will be included as a variation factor in the analysis.

8 Management of Investigational Medicinal Product and Reference Product

Tolvaptan OD tablet 15 mg and tolvaptan OD tablet 30 mg are the test products and provided to this study as IMPs. Tolvaptan conventional tablet 15 mg and tolvaptan conventional tablet 30 mg will be used as the reference products.

For full details on Management of the IMPs and reference products, please refer to the IB and Clinical Operation Manual.

8.1 Packaging and Labeling

The IMP and reference products will be provided to the IMP manager by the sponsor or designated agent. The IMP will be supplied as bottles. Each bottle will be labeled to clearly disclose that the contents are for clinical trial use, protocol number, IMP name,

quantity, lot number, expiration date, storage condition, and sponsor's name and address. The reference products will be provided in commercial packaging.

8.2 Storage

The IMP and reference product will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager. No IMP manager may provide IMP or reference product to any subject not participating in this protocol.

Both the IMP and reference product will be stored at room temperature.The clinical site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.

8.3 Accountability

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

8.4 Returns and Destruction

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

All IMP and reference product returned to the sponsor must be accompanied by appropriate documentation and be identified by protocol number with trial site number on the outermost shipping container. Returned supplies should be in the original containers. The assigned trial monitor will facilitate the return of unused and/or partially used IMP and reference product.

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 a drug product/reference product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of the IMP or reference 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 defects (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 or IMP manager must record all PQCs identified through any means from the receipt of the IMP and reference product from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or IMP manager must notify the sponsor by e-mail immediately after becoming aware of the PQC according to the procedure outlined below.

- PQC_156-102-00136@otsuka.jp
  Send the information identified in (Section 8.5.2, Information Required for Reporting Purposes) to the above email address.

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

8.5.2 Information Required for Reporting Purposes

- Description of compliant
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return to the sponsor. If necessary, the sponsor will specify the return procedure.

8.5.4 Assessment/Evaluation

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

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments.

All source documents pertaining to this trial will be maintained by the trial site and made available for direct access by authorized persons. Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF.

9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each clinician (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 the trial progress notes and other source documents will be initialed and dated on the day the change is made by a site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the

clinician. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

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

9.3 File Management at the Trial Site

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

9.4 Records Retention at the Trial Site

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

- The date 2 years after 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 results of the trial will not be submitted with the approval application, the date 3 years after receipt of such notification.
- The date 3 years after termination or completion of the trial.

The trial site must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The trial site will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently

via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

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

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

11 Ethics and Responsibility

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

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject identifier 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, subject to 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 will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(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 local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

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

14 Publication Authorship Requirements

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

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND

4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

Investigators or other trial 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

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3 International Conference on Harmonization (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.

4 Otsuka Pharmaceutical. OPC-41061 (Tolvaptan) Investigator's Brochure (Japanese Translation), edition 17 (Japan). Otsuka report, issued 25 Aug 2015.

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