STATISTICAL ANALYSIS PLAN

A Single-center, Open-label, Randomized, 3-Period, 3-Way, Crossover Bioequivalence Study of Tolvaptan 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)

Protocol No. 156-102-00136

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

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CONFIDENTIAL – PROPRIETARY INFORMATION

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AUC_t	Area under the concentration-time curve from time zero to the last observable concentration at time t
AUC_∞	Area under the concentration-time curve from time zero to infinity
AUC_% Extrap	Percentage of AUC due to extrapolation from tlast to infinity $[(AUC_\infty - AUC_t) / AUC_\infty \times 100]$
BMI	Body mass index
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
CV	Coefficient of variation
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
MRT_∞	Mean residence time from time zero to infinity
OD	Orally disintegrating
OPC	Otsuka Pharmaceutical Co
PT	Preferred Term
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
SOC	System Organ Class
$t_{1/2,z}$	Terminal-phase elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum [peak] plasma concentration
t_{last}	Time of last measurable [positive] concentration
λ_z	Apparent terminal-phase disposition rate constant (first-order)

1 Introduction

This statistical analysis plan documents the details of the statistical analysis methodology to be applied in Study 156-102-00136.

2 Trial Objectives

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

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 of the protocol, "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.

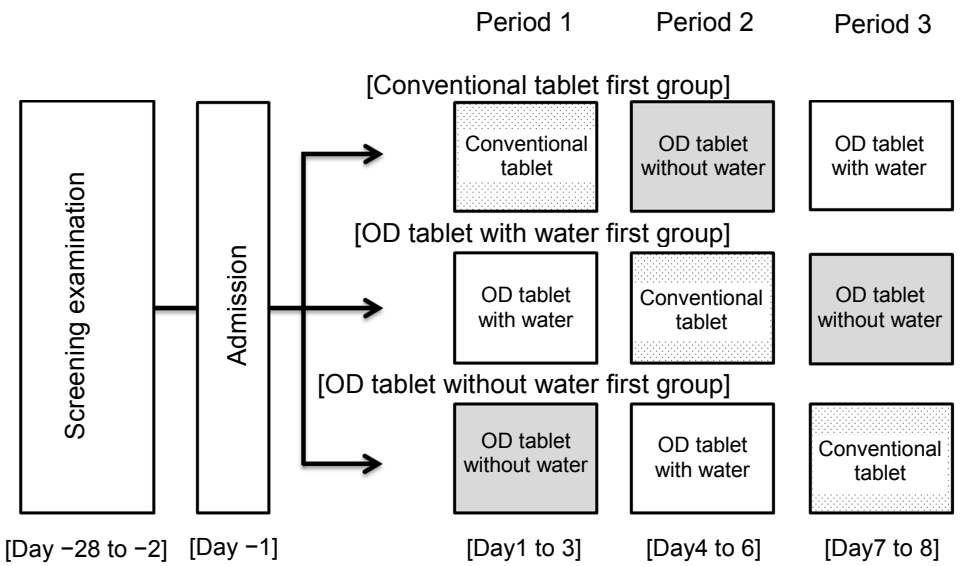

Figure 3.1-1 Trial Design Schematic

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).

3.3 Trial 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.

3.4 Handling of Time Points

Data measured at the time points specified in the protocol will be used. Examinations specified for discontinuation and unscheduled examinations will be presented in lists, but will not be used in summaries.

4 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) [2] 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.

5 Statistical Analysis Sets

5.1 Efficacy Analysis Set

No efficacy analysis will be performed in this trial.

5.2 Safety Analysis Set

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

5.3 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.

5.4 Handling of Missing Data

Missing values will not be imputed.

6 Primary and Reference Endpoint Variables

6.1 Primary Variables

AUC_t and C_{max} of tolvaptan

6.2 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

6.3 Subject Disposition

The number of screened subjects will be summarized. In each cohort, overall and for each group (the conventional tablet first group, OD tablet with water first group, and OD tablet without water first group), the number of randomized subjects, the number of subjects administered IMP, the number of completed subjects, and the number of

discontinued subjects will be summarized. The percentages of subjects with each reason for discontinuation relative to the number of randomized subjects will be summarized.

The numbers of subjects included in the bioequivalence analysis set and safety analysis set, and the percentages of these subjects relative to the number of randomized subjects, will be summarized for each cohort, overall, and for each group.

6.4 Demographic and Other Baseline Characteristics

For the bioequivalence analysis set and safety analysis set, descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) of the age, height (cm), body weight at screening (kg), and BMI (kg/m^2) will be calculated in each cohort, overall and for each group. Distributions (numbers of subjects, %) of the history of smoking and history of alcohol consumption will be calculated.

6.5 Medical History

For the bioequivalence analysis set and safety analysis set, distributions for presence or absence of medical history and current symptoms will be calculated in each cohort, overall and for each group.

6.6 Investigational Medicinal Product Compliance

This will not be summarized in this trial.

6.7 Prior and Concomitant Medication

This will not be summarized in this trial.

6.8 Protocol Deviations

Distributions will be calculated for each type of significant deviation from the protocol in each cohort.

7 Efficacy Analysis

Not applicable.

8 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.

8.1 Extent of Exposure to Investigational Medicinal Product

The percentages of subjects administered IMP relative to the number of randomized subjects will be calculated, by formulation and dosing regimen, overall and in each group.

8.2 Adverse Events

All adverse events (AEs) will be coded by system organ class (SOC) and preferred term (PT) (Medical Dictionary for Regulatory Activities [MedDRA] version 20.0). The incidence of the following events in subjects administered IMP using the relevant formulation and dosing regimen will be summarized for all events, by SOC, and by PT.

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

AEs that emerge after IMP administration in Periods 1 and 2 up to predose in the next period will be regarded as TEAEs in Periods 1 and 2, respectively. AEs that emerge after IMP administration in Period 3 will be regarded as TEAEs in Period 3. If there are multiple occurrences of the same event in the same period in the same subject, the event with the highest severity will be selected. The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

8.3 Clinical Laboratory Data

For each parameter (excluding qualitative urine tests), descriptive statistics of measurements and changes from baseline at each time point will be calculated. 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.

For qualitative urine tests, a shift table comparing results to baseline by time point will be created.

8.4 Vital Sign

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

8.5 Physical Examination

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

8.6 Electrocardiogram Data

For each 12-lead electrocardiogram (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. For corrected QT intervals (QTcF and QTcB), the number and percentage of subjects meeting the following conditions will be calculated.

- Subjects with measurements "> 0.450 seconds," "> 0.480 seconds," and "> 0.500 seconds"
- Subjects with changes from baseline "> 0.030 seconds" and "> 0.060 seconds"

8.7 Body Weight

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

9 Pharmacokinetic Analysis

The following analyses will be performed for the bioequivalence analysis set per cohort. Sensitivity analysis of the primary variable will be performed on subjects for whom evaluable AUC_t and C_{max} values were obtained in Periods 1, 2, or 3.

9.1 Statistical Analysis of Primary Variables

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 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 with the pooled data of both the main study and add-on subject study, using the study as a variation factor.

3) When there are discontinued subjects or unevaluable data, a sensitivity analysis will be performed. Log-transformed AUC_t and C_{max} values will be analyzed with a linear mixed-effects model, using group, administration period, and formulation and dosing regimen as fixed effects and subjects within group as a random effect, and the difference between formulations (OD tablet without water − conventional tablet and OD tablet with water − conventional tablet) and corresponding 90% confidence intervals will be calculated.

9.2 Statistical Analysis of Reference Variables

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%.

9.3 Methods of Pharmacokinetic Analysis

9.3.1 Blood Collection Time Points

In each period, before IMP administration and 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 hours postdose

9.3.2 Method of Calculating Pharmacokinetic Parameters

1) AUC_t, C_{max}, AUC_∞, MRT_∞, t_{max}, λ_z, AUC_% Extrap, $t_{1/2,\,z}$, t_{last}, CL/F, λ_z (point), λ_z (lower), λ_z (upper) and λ_z (Rsq) are to be calculated per subject by non-compartmental analysis.
2) CL/F/BW is to be calculated by dividing CL/F by the body weight (kg) before IMP administration in each period.
3) 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).
4) 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.

9.4 Technical Details of Pharmacokinetic Statistical Analysis

9.4.1 Exclusion From Pharmacokinetic Analysis

9.4.1.1 Blood Collection Time Points Outside the Acceptable Time Windows

If blood is collected at a time point outside the acceptable time window, and it is determined that the data is unsuitable for calculation of descriptive statistics for plasma concentrations, the data will be excluded from the calculation of descriptive statistics for plasma concentrations while it will be included in pharmacokinetic analysis.

9.4.1.2 In the Event Vomiting Occurs

With reference to the Food and Drug Administration (FDA) guidance,[3] if vomiting occurs at a time point less than twice the median t_{max}, the data for this period for the subject who experienced vomiting will be excluded from pharmacokinetic analysis. The median t_{max} that is referenced for that judgment is the median of the same group in the same studycalculated excluding the vomiting case.

9.4.1.3 In the Event Prohibited Medications Are Used

If prohibited medications that may affect the pharmacokinetics of IMP are used, data points after the use of prohibited medications in the relevant subjects will be excluded from pharmacokinetic analysis.

9.4.2 Reporting of Concentrations and Parameters

1) Values below the lower limit of quantitation occurring at time points before the first quantified level for drug concentration will be treated as 0.
2) Values below the lower limit of quantitation occurring at time points after the first quantified level for drug concentration will be treated as missing.
3) Descriptive statistics for parameters listed in Section 6.2 1) will be calculated at each blood collection point, for each cohort, for administration of the conventional tablet, OD tablet without water, and OD tablet with water. Descriptive statistics for parameters listed in Sections 6.1 and 6.2 2) will be calculated for each parameter, for each cohort, for administration of the conventional tablet, OD tablet without water, and OD tablet with water. The descriptive statistics calculated for plasma drug concentration will be number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum, the descriptive statistics calculated for parameters other than t_{max} and t_{last} will be number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum, and the descriptive statistics calculated for t_{max} and t_{last} will be number of subjects,

minimum, median, and maximum. Descriptive statistics will not be calculated for λ_z (Rsq), λ_z (point), λ_z (upper), or λ_z (lower).

4) Arithmetic means and standard deviations will be used to plot plasma concentration-time profile.
5) Individual values and descriptive statistics for pharmacokinetic parameters are displayed using the number of digits presented in Table 9.4.2-1. Coefficient of variation (CV%), which is used as a descriptive statistic, will be rounded off to 1 decimal place.

Table 9.4.2-1 Handling of Numerical Values

AUC_t, AUC_∞	3 significant figures
AUC% Extrap	1 decimal place
C_{max}	3 significant figures
CL/F, CL/F/BW	3 significant figures
MRT_∞	1 decimal place
t_{max}	1 decimal place
t_{last}	1 decimal place
$t_{1/2,z}$	1 decimal place
λ_z	3 significant figures
λ_z (point)	Whole numbers
λ_z (lower), λ_z (upper)	2 decimal places
λ_z (Rsq)	4 decimal places
Geometric mean ratio (GMR)	4 decimal places
Confidence interval of GMR	4 decimal places
By-subject ratio	2 decimal places
Difference in t_{max} by subject	1 decimal place

10 Pharmacodynamic Analysis

No pharmacodynamic analysis will be performed in this trial.

11 Pharmacogenomic Analysis

No pharmacogenomic analysis will be performed in this trial.

12 Interim Analysis

None.

13 Changes in Planned Analysis

No notable changes.

14 References

1 Guidelines for Bioequivalence Studies of Generic Products, PFSB/ELD Notification No. 0229-10 (29 Feb 2012).

2 Diletti E, Hauschke D, Steinijans WV. Sample size determination for bioequivalence assessment by means of confidence intervals. International J. of Clinical Pharmacology, Therapy, and Toxicology. 1991;29(1),1-8.

3 Food and Drug Administration. Guidance for industry: bioavailability and bioequivalence studies for orally administered drug products - general considerations. Food and Drug Administration. 2003 revision 1.