STATISTICAL ANALYSIS PLAN

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

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Otsuka Pharmaceutical Co., Ltd.

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OPC-61815

Protocol No. 263-102-00005

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Statistical Analysis Plan

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
BMI	Body mass index
CRF	Case report form
CYP	Cytochrome P450
ECG	Electrocardiogram
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
QT	QT interval
QTc	QT corrected for heart rate
SAE	Serious adverse event
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

Pharmacokinetics Parameter Table

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

1 Introduction

This statistical analysis plan documents the details of the statistical analysis methodology to be applied in the protocol of Study 263-102-00005.

2 Trial Objectives

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

3 Trial Design

3.1 Type/Design of Trial

This is a single-center, randomized, double-blind, placebo- and moxifloxacin active-controlled, 4-period crossover trial in 48 healthy adult male subjects. OPC-61815 and placebo will be administered in a double-blind fashion and moxifloxacin tablets will be administered in an open-label fashion, and the effects of 16 mg and 32 mg OPC-61815 on the QT/QTc interval will be evaluated.

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

3.2 Trial Treatments

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

on Day 2 is at least 6 days before IMP administration in the next treatment period. Post-treatment follow-up will be performed 6 to 8 days after IMP administration in Period 4.

3.3 Trial Population

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

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

3.4 Handling of Time Points

CRF Visit values and Time point values at each time point (after the day before administration) will be used in summaries (but values at the time of discontinuation will not be used in summaries). Unscheduled Visit values will not be used.

4 Sample Size

The number of subjects required for central tendency analysis of QTcF, the primary endpoint, was calculated. The number of subjects was calculated to achieve a ≥90% probability of the upper limit of the 2-sided 90% CI (1-sided 95% CI) for the time-matched difference in the mean values for the change in QTcF from baseline between the OPC-61815 and placebo values being lower than 10 msec at all time points after administration of each OPC-61815 dose (16 and 32 mg), and a ≥90% probability of the lower limit of the 2-sided 98% CI (1-sided 99% CI) for the time-matched difference in the mean values for the change in QTcF from baseline between the moxifloxacin and placebo values being higher than 0 msec in at least one of the 5 assay sensitivity assessment time points (1, 1.5, 2, 3, and 4 hours) after administration of the positive control moxifloxacin. For the assay sensitivity CI, the increase of type 1 error due to the multiplicity of multiple time points was corrected using the Bonferroni method.

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

5 Statistical Analysis Sets

5.1 Pharmacodynamic Analysis Set

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

5.2 Safety Analysis Set

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

5.3 Pharmacokinetic Analysis Set

Pharmacokinetic analysis set includes subjects who are included in the safety analysis set and whose plasma drug concentration was measured. However, plasma drug concentrations will not be measured for placebo and moxifloxacin administration.

5.4 Handling of Missing Data

No data imputation will be performed for missing data.

6 Primary and Secondary Outcome Variables

6.1 Primary Outcome Variables

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

6.2 Secondary Outcome Variables

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

6.3 Pharmacokinetic Outcome Variables

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

6.4 Safety Outcome Variables

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

7 Disposition and Demographic Analysis

7.1 Subject Disposition

For subjects from whom informed consent was obtained (screened subjects), the number of subjects whom informed consent was obtained, the numbers and percentages of randomized subjects, subjects administered IMP, completed subjects after IMP administration, and discontinued subjects after IMP administration (the denominator indicates the number of randomized subjects) will be summarized as a whole and per sequence. For discontinued subjects after IMP administration, the number and percentage of subjects by reason for discontinuation will be summarized.

For randomized subjects, the number and percentage of subjects included in each statistical analysis set and central tendency analysis (11.1.1 Primary Endpoints Analysis) will be summarized as a whole and per sequence.

7.2 Demographic and Baseline Characteristics

For the pharmacodynamic analysis set and the safety analysis set, descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) for age, height (cm), body weight (kg) at screening, and BMI (kg/m^2) will be calculated as a whole and per sequence.

7.3 Medical History

For the pharmacodynamic analysis set and the safety analysis set, frequency distribution (number of subjects, %) of the presence or absence of medical history and complications will be calculated as a whole and per sequence.

7.4 Treatment Compliance

For the pharmacodynamic analysis set and the safety analysis set, frequency distribution of subjects who satisfy all the following conditions for each treatment (OPC-61815 16 mg, OPC-61815 32 mg, placebo, or moxifloxacin) will be calculated by treatment as a whole and per sequence.

- Injection (OPC-61815 16 or 32 mg, or placebo)
  - Single intravenous administration over a period of 1 hour (allowable time range: 59 to 65 minutes) once daily in a fasting state.
  - Administration of full dose of IMP completed within allowable time range.
  - No interruption of administration from 30 minutes after the start.
- Tablet (moxifloxacin)
  - Administration of full dose of IMP completed.

7.5 Prior and Concomitant Medication

Prior and concomitant medications will not be tabulated in this trial.

7.6 Protocol Deviations

Protocol deviations will not be tabulated in this trial.

8 Efficacy Analyses

Not applicable.

9 Safety Analyses

The following analyses will be performed per treatment in the safety analysis set. The baseline will be the value before the start of IMP administration on Day 1 in each treatment period.

9.1 Extent of Exposure

The percentage of administered subjects to randomized subjects will be calculated.

9.2 Adverse Events

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

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuations of the IMP (calculated only when treatment is injection)

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

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

9.3 Clinical Laboratory Data

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

9.4 Vital Sign Data and Body Weight

For each item (blood pressure, pulse rate, body temperature, and body weight), descriptive statistics will be calculated for measurements and changes from baseline at each postdose time point.

9.5 Physical Examination Data

Physical findings will not be tabulated in this trial.

9.6 Electrocardiogram Data

For each parameter (heart rate, RR interval, PR interval, QRS interval, QT interval and QTcF interval) of 12-lead electrocardiogram (ECG), descriptive statistics will be calculated for measurements and changes from baseline at each postdose time point. On normal/abnormal assessment, a shift table comparing data at each postdose time point to baseline will be created.

10 Pharmacokinetic Analyses

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

      [a]Calculated for OPC-61815 only

2) Handling of Data
   a) Nonacceptance of data will be determined in accordance with the following conditions in this trial.
      - For each analyte, if blood sampling is conducted outside the time window for the analyses (see Table 10-1~~Table 10-1~~ and Table 10-2~~Table 10-2~~), the data will be excluded from the calculation of descriptive statistics for plasma concentrations at that time point. However, it will be used for the

calculation of pharmacokinetic parameters, and if the calculation of pharmacokinetic parameters is determined to be unsuitable, the parameter will not be adopted.

Table 10-1 Acceptable Window for Analysis of OPC-61815 (Same in each period)

Time Point		Acceptable Window
Day 1	Predose	Within 3 hours before IMP administration
	1 hour	Within 2 minutes after end of administration
	1.5 hours	Specified time point + 2 minutes
	2 hours	Specified time point + 3 minutes
	3 hours	Specified time point + 5 minutes
	4 hours	Specified time point + 10 minutes
	6 and 12 hours	Specified time point + 15 minutes
Day 2	24 hours	Specified time point + 30 minutes

Table 10-2 Acceptable Window for Analysis of OPC-41061 (Same in each period)

Time Point		Acceptable Window
Day 1	Predose	Within 3 hours before IMP administration
	1 hour	Within 2 minutes after end of administration
	1.5 hours	Specified time point + 10 minutes
	2 hours	Specified time point + 10 minutes
	3 hours	Specified time point + 10 minutes
	4 hours	Specified time point + 10 minutes
	6 and 12 hours	Specified time point + 15 minutes
Day 2	24 hours	Specified time point + 30 minutes

- None of the plasma concentrations after use of drugs or food (see Appendix 4~~Appendix 4~~) which may inhibit or induce CYP3A4 activity will be used for calculating descriptive statistics at that time. Of the parameters calculated with data including plasma concentrations excluded from descriptive statistics, the parameters determined to be unsuitable for the calculations will not be adopted.
- For OPC-61815 injection 16 mg and 32 mg groups, in the case that IMP administration was not performed by the following administration method or in the event of missing a dose, the plasma concentrations on the period (treatment) will not be used for the calculation of descriptive statistics. The parameters calculated with data including plasma concentrations excluded from descriptive statistics will not be adopted.
  - Single intravenous administration over a period of 1 hour (allowable time range: 59 to 65 minutes) once daily in a fasting state
  - Administration of full dose of IMP completed within allowable time range.
  - No interruption of administration from 30 minutes after the start.

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b) Plasma concentrations below lower limit of quantitation that occur prior to and after the first measurable concentration will be imputed to 0 (ng/mL) and as missing, respectively. Lower limit of quantitation of each analyte is listed in Appendix 5~~Appendix 5~~.

c) Concentrations reported as Not Analyzed (NA) or Not Determined (ND) are regarded as missing values.

d) Unused concentrations and the unadopted parameters should be outputted in the list.

e) Missing or unused concentrations and parameter values that cannot be calculated or adopted will not be used for tabulation.

3) Statistical analysis method

Descriptive statistics will be calculated in the following manner:

a) Plasma drug concentration

- At each blood collection time point, descriptive statistics will be calculated by analyte and treatment.
- Descriptive statistics to be calculated for plasma drug concentration will be number of analyzed subjects, number of subjects included in the tabulation, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum. However, descriptive statistics will be calculated only at the time point when the number of subjects included in the tabulation exceeds half of the number of analyzed subjects.

b) Plasma pharmacokinetic parameters excluding λ_z, λ_z(lower), λ_z(upper), λ_z(point), and λ_z(Rsq)

- Descriptive statistics will be calculated for each parameter by analyte and treatment.
- Descriptive statistics to be calculated for plasma drug concentration will be number of analyzed subjects, number of subjects included in the tabulation, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum. However, descriptive statistics will be calculated only when the number of subjects included in the tabulation exceeds half of the number of analyzed subjects.

10.1 Statistical Analyses of Primary Pharmacokinetic Endpoints

Not applicable.

10.2 Statistical Analyses of Secondary Pharmacokinetic Endpoints

Not applicable.

10.3 Technical Details of Pharmacokinetic Statistical Analyses

Not applicable.

10.4 Pharmacokinetic and Pharmacodynamic Analyses

For subjects who have QT data and plasma OPC-61815 concentration data after administration of OPC-61815 (adopted concentration at 10 Pharmacokinetic Analyses 2) Handling of Data), as well as QT data after placebo administration at the matching time points, differences between OPC-61815 and placebo in change in QTcF interval from baseline at the matching time points are analyzed. A linear mixed-effects model is used, taking plasma OPC-61815 concentration as a fixed effect and subject as a random effect (slope and intercept), to estimate the intercept and the coefficient of plasma OPC-61815 concentration. A scatter plot of plasma OPC-61815 concentrations (horizontal axis) and the time-matched differences (vertical axis) between the OPC-61815 and placebo data in change from baseline for QTcF will be created and a regression line will be plotted.

SAS code is shown below.

```
proc mixed method=reml;
  class subject;
  model corrected_QTcF = conc / s alpha=0.05;
  random int conc / subject=subject type=vc;
run;
```

11 Pharmacodynamic Analyses

12-lead Holter ECG data will be used. For each parameter, the mean (rounded integer value in each unit [beats/min, msec]) of measurements from 3 predose time points (1 hour, 30 minutes, and 15 minutes before IMP administration) in each period will be used as the baseline value. If missing is occurred at any of 3 predose time points in each period, a mean value will be calculated using the points at which the values were obtained and will be used as the baseline value. Changes from baseline in corresponding period will be calculated at each postdose time point.

11.1 Primary and Secondary Endpoint Analyses

11.1.1 Primary Endpoint Analyses

The primary endpoint is the time-matched difference between the OPC-61815 and placebo data in change from baseline for QTcF in 12-lead Holter ECG. Central tendency analysis for OPC-61815 will be performed for subjects in the pharmacodynamic analysis set who appropriately completed all IMP treatments (OPC-61815 16 mg, OPC-61815 32 mg, placebo, and moxifloxacin) (ie, in whom the administration of the injections was completed within the time windows presented in Protocol 3.2 Trial Treatments [the duration of intravenous administration of OPC-61815 16 mg or 32 mg or placebo: 59 to

65 minutes] without interruption of administration from 30 minutes after the start, as well as the condition described in 7.4 Treatment Compliance) and for whom predose and postdose QT data are available for all 4 treatment periods.

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

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

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

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

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

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

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

SAS code is shown below. The data set will include all 4 treatments data.

```
proc mixed method=reml;
  class treatment subject time arm period;
  model change = arm period treatment time treatment*time baseline/ s ddfm=satterth;
  random subject(arm);
  lsmeans treatment*time/diff pdiff cl alpha=0.1;
run;
```

11.1.2 Secondary Endpoint Analysis

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

11.1.2.1 Categorical Analysis

The number and percentage of subjects who fulfilled the following criteria for QTcF interval at least once after IMP administration are calculated. The same calculation will also be performed at 3 predose time points and each postdose time point for 1), and at each postdose time point for 2).

1) Prolongation of absolute QTc interval:
   QTc interval > 450 msec
   QTc interval> 480 msec
   QTc interval> 500 msec
2) Change from baseline in QTc interval:
   > 30 msec increase in QTc interval from baseline
   > 60 msec increase in QTc interval from baseline

11.1.2.2 Electrocardiogram (12-lead Holter Electrocardiogram)

For each parameter (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval), descriptive statistics will be calculated for measurements and changes from baseline at each time point.

A shift table of normal/abnormal assessments at each postdose time point compared to baseline will also be created. In a triplicate 12-lead ECG at each time point, an ECG parameter will be assessed as “normal” only when all 3 measurements are normal; otherwise it will be assessed as “abnormal” (ie, if any measurement is abnormal). In baseline assessment of 12-lead Holter ECGs at 3 predose time points (1 hour, 30 minutes, and 15 minutes before IMP administration) in each period, an ECG parameter will be assessed as “normal” only when all measurements at 3 predose time points are normal; otherwise it will be assessed as “abnormal” (ie, if any measurement is abnormal).

For the electrocardiographic waveform pattern, the number and percentage of subjects satisfying each Change Relative to Baseline at least once after IMP administration based on Criteria for Identifying ECG Measurements of Potential Clinical Relevance (Appendix 1~~Appendix 1~~) will be calculated. The same calculation will also be performed at each time point.

11.1.3 Assay Sensitivity Assessment

As an assay sensitivity assessment, moxifloxacin will be evaluated as a positive control using the same analysis set, data set, and statistical method as those stated in 11.1.1 Primary Endpoint Analyses.

For moxifloxacin, the lower limit of the CI for the time-matched difference in the least squares mean for the change in QTcF from baseline compared to the placebo data will be evaluated if it is higher than 0 msec at any of the postdose time points using the hypothesis presented below. Because of the multiplicity arising from assay sensitivity assessments at 5 postdose time points (1, 1.5, 2, 3, and 4 hours), type 1 error adjustment will be performed using the Bonferroni method, and the 2-sided 98% (1-sided 99%) CI will be calculated (alpha = 0.02 in SAS code in 11.1.1 Primary Endpoint Analyses).

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

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

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

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

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

12 Pharmacogenomic Analyses

No pharmacogenomic analysis will be performed.

13 Interim Analysis

No interim analysis will be performed.

14 Changes in Planned Analysis

- For omission in entry, "V_Z/BW" was added in Protocol 6.1.2 (1) Endpoints.
- For erroneous entry, "Apparent" in the definition of "V_Z" in the Pharmacokinetics Parameter Table was deleted.

15 References

None.