Official Title: **A SINGLE-CENTER, NON-RANDOMIZED, OPEN-LABEL, ONE-SEQUENCE, TWO-PERIOD WITHIN-SUBJECT STUDY TO INVESTIGATE THE EFFECT OF RIFAMPICIN ON THE PHARMACOKINETICS OF MULTIPLE DOSES OF BALOVAPTAN IN HEALTHY VOLUNTEERS**

NCT Number: NCT03586726

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Statisti cal Analysis Plan

Sponsor:	F. Hoffmann-La Roche Ltd
Protocol No:	WP40608
Protocol Title:	A SINGLE-CENTER, NON-RANDOMIZED, OPEN-LABEL, ONE-SEQUENCE, TWO-PERIOD WITHIN-SUBJECT STUDY TO INVESTIGATE THE EFFECT OF RIFAMPICIN ON THE PHARMACOKINETICS OF MULTIPLE DOSES OF BALOVAPTAN IN HEALTHY VOLUNTEERS
PRA Project ID:	RPU034EC-180341
Version Date:	04-Oct-2018

1.0 Approv als

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	[redacted] / Biostatistician
Signature of Sponsor Representative / Date:	08-Oct-2018 [redacted]
Name of Author / Title:	[redacted] / Biostatistician
Signature of Author / Date:	[redacted] Signed by: [redacted] Biostatistician Reason: I am approving this document Date & Time : 09 Oct 2018 05:16 PM +02:00

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under F. Hoffmann-La Roche Ltd Protocol WP40608.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 03-Jun-2018 (including all amendments up to this protocol date) and the final eCRF(s) dated 02-Jun-2018.

An approved and signed SAP is a requirement for database lock.

This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the pharmacokinetic (PK) and safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in Section 9.8.2 of the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

This study will investigate the effect of rifampicin treatment on the PK of balovaptan and its major metabolites M2 and M3.

5.1 Primary Objective

To investigate the effect of multiple doses of rifampicin, a potent cytochrome P450 (CYP)3A4 inducer, on the PK of balovaptan 10 mg once daily (qd) and its major metabolites M2 and M3 at steady state in healthy subjects.

5.1.1 Primary Endpoints

PK parameters for balovaptan, M2, and M3 following 10 days of qd dosing of balovaptan 10 mg:

- Maximum observed plasma concentration (Cmax)
- Area under the plasma concentration curve from time 0 to 24 hours (AUC0-24h)

5.2 Secondary Objectives

- To evaluate the safety and tolerability of balovaptan 10 mg qd administered alone and in combination with rifampicin in healthy subjects.
- To investigate the effect of multiple doses of rifampicin on secondary PK parameters of multiple doses of balovaptan 10 mg qd and its major metabolites M2 and M3 at steady state in healthy subjects.

5.2.1 Secondary Endpoints

Safety and tolerability:

- Adverse events (AEs)
- Clinical laboratory values

- Vital signs
- Electrocardiogram (ECG)
- Columbia-Suicide Severity Scale (C-SSRS)
- Physical examination

Secondary PK parameters for balovaptan and metabolite M2 and M3:

- Time to maximum observed plasma concentration (t_{max})
- Metabolite to parent ratio
- Any other parameter as appropriate (see Table 1)

5.3 Tertiary/ Exploratory Objectives

To evaluate the plasma exposure of rifampicin 600 mg qd.

To investigate the relationship between the CYP3A4 genotype and steady state balovaptan exposure, and the influence of the CYP3A4 genotype on the effect of rifampicin on balovaptan PK. The relationship between other genotypes and PK of balovaptan may also be explored.

5.3.1 Tertiary/Exploratory Endpoints

Exploratory PK parameters for rifampicin following 6 and 16 days of qd dosing:

- C_{max}
- AUC0-24h
- t_{max}
- AUC0-last
- any other parameter as appropriate (see Table 1)

The pharmacogenetics of metabolizing enzymes, tranferases, transporters, etc, possibly involved in the absorption, distribution, metabolism and excretion of balovaptan and its major metabolites (e.g., CYP3A and P-glycoprotein). Results may be pooled with data from other studies of balovaptan.

6.0 Study Design

This study will be a single-center, non-randomized, open-label, one-sequence, two-period, within-subject study to investigate the effects of multiple doses of rifampicin on the PK and safety of multiple doses of balovaptan in healthy subjects. The study will be conducted at 1 site in the Netherlands.

Screening will be conducted up to 3 weeks prior to admission in the clinical research unit (CRU). Subjects will be in the CRU for 2 study periods. In both periods, subjects will be admitted on Day -1 (the day before dosing begins); Day 1 will be the first day of dosing. In Period 1, subjects will be discharged on Day 11 after the last assessment is completed. There will be a minimum of a 14-day to a maximum of a 21-day washout between the last dose in Period 1 and the first dose in Period 2. Subjects will therefore return to the CRU on Day 24 or up to Day 30 of Period 1 (Day -1 of Period 2) to begin Period 2. In Period 2, subjects will be discharged on Day 17 after all assessments have been performed. Subjects will return for a follow-up visit between 14 to 21 days after the last dose.

Subjects will receive the following study drugs in the 2 study periods, after an overnight fast of at least 8 hours:

Study Period 1:

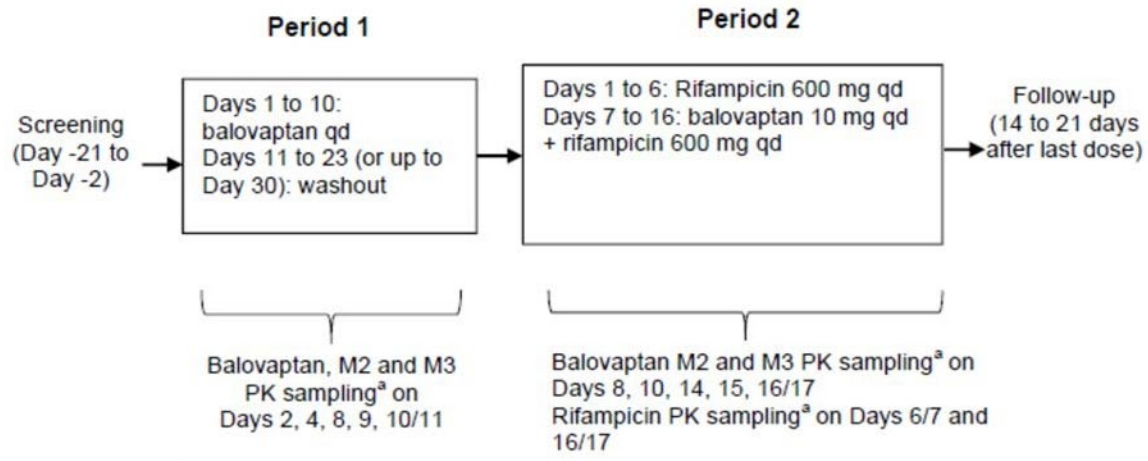
- Days 1 to 10: oral balovaptan 10 mg qd
- Days 11 to 23 (or up to Day 30): no study drug

Study Period 2:

- Days 1 to 6: rifampicin 600 mg qd
- Days 7 to 16: balovaptan 10 mg qd + rifampicin 600 mg qd

Figure 1 presents an overview of the study design.

Figure 1: Study Schema



Abbreviations: PK = pharmacokinetic; qd = once daily;
[a]Full balovaptan PK profile on Day 10/11 of Period 1 and Day 16/17 of Period 2; trough concentrations on other days. Full rifampicin PK profile on Days 6/7 and 16/17 of Period 2

A total of 16 subjects will be enrolled to ensure 12 evaluable subjects.

6.1 Sample Size Considerations

This is an exploratory study for which no formal statistical hypothesis will be tested. Therefore, the sample size is chosen to estimate with sufficient precision the effect of CYP3A4 induction on balovaptan.

The sample size of 12 evaluable subjects was chosen based on balovaptan within-subject variability (CV%) of around 39% for AUC0-24h and 36% for Cmax as obtained from the 12 mg repeat dose in study BP25694. Based on the higher value of 39%, it was estimated that with 12 subjects the half-width of the 90% confidence interval (CI) for the ratio of treatment geometric means of the combination (balovaptan + rifampicin) versus balovaptan alone would be obtained by dividing/multiplying the ratio estimate by a factor of 1.30.

6.2 Randomization

Not applicable, this is a non-randomized study.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

There are no changes from the protocol.

7.2 Interim Analysis and Key Results

No interim reporting is planned for this study.

7.3 Final Analysis

Draft TFLs will be provided with the draft CSR. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the final CSR.

8.0 Data Review

8.1 Data Management

Data handling, transfer and coding will take place under the PRA Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, all data (except the PK data) will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

For descriptive statistics of safety data, range values will be presented with the same precision (number of decimals or significant digits) as the data they are calculated from, median, arithmetic mean values with 1 more decimal digit, standard deviation (SD) with 2 more decimal digits. Percentages will be rounded to integers.

For the derived PK parameters Appendix 2 of the Roche Clinical Pharmacology Guideline will be followed [3]. For all PK parameters except t_{max}; individual subject data, range values, median, arithmetic mean, geometric mean and standard deviation (SD) will be presented with a precision of 3 significant digits. The coefficients of variation (CV) with 1 decimal digit.

All individual data and descriptive statistics for t_{max} will be reported with 2 decimals, except for the CVs which will be presented with 1 decimal digit.

9.1.2 Imputation

Except for the substitution of any PK concentrations below the lower limit of quantification (LLOQ) (see Section 16.2) and missing start or end date/times of Adverse Events (AEs) for the calculation of onset and duration (see Section 17.1.1), any missing data will not be imputed.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics:

- n (number of observations),

- nmiss (number of missing observations),
- (arithmetic) mean,
- SD,
- minimum (min) value,
- median, and
- maximum (max) value.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data the categories will be presented in the tables exactly as they appear in the CRF / Database.

9.1.4 Pooling

Summary statistics will be calculated by treatment (and time point, if applicable).

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. Except for unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations within each period is defined as the last observation recorded before the first study drug administration in each period. The last observation can be an unscheduled / repeated measurement. Baseline for Electrocardiograms (ECGs) is derived as the mean of the triplicate pre-dose measurements of pre-dose assessments taken in Analysis Period 1.

9.2.2 Treatment Grouping

Period will refer to the analysis (treatment) period, as opposed to study period. This means that Study Period 2 will be divided in two analysis periods, Analysis Period 2 (Days -1 to 6) and Analysis Period 3 (Days 7 to 16). The study will therefore consist of 3 analysis periods. For Analysis Period 3, the analysis day will also be adjusted by subtracting 6 from the study day. Thus, Period 3 will have Analysis Days 1 to 10.

Label	Grouping
Analysis Period	
Study Drug	Balovaptan (reference), rifampicin, balovaptan + rifampicin (test)
Treatment	Treatment S: 10 mg balovaptan Treatment I: 600 mg rifampicin Treatment S+I: 10 mg balovaptan + 600 mg rifampicin

S= Substrate, I= Index Inducer

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation	Note
Change from Baseline	All	Post-dose Observation minus Baseline Observation	
Analysis Period	All	Time period starting 1 day before dosing of each of the treatments and ends 1 day before dosing in next analysis period or at the start of the follow-up period for the last treatment.	
Analysis Study Day (Prior to Dose)	All	Date of Measurement minus Dose Date	
Analysis Study Day (Post Dose)	All	Date of Measurement minus Dose Date +1	

9.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the general PRA EDS QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. As the primary objective of this study is to characterize the PK the datasets considered critical are subject level and PK (ADSL, ADPC, ADPP). As these are related to the primary objectives these datasets will be double programmed per the QC Plan.

9.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1. At least the following datasets will be created:

- ADSL
- ADAE
- Laboratory Analysis Dataset (ADLB)
- Vital Signs Analysis Dataset (ADVS)
- ECG Analysis Dataset (ADEG)
- ADPC
- ADPP

ADaM compliant datasets will be delivered to the sponsor. A define.xml file Version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® Version 8.1 or higher ([redacted]). Additional PK computations may be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

CYP3A4 genotype will be investigated as a factor in this study. PK tables will be presented by CYP3A4 genotype.

The pharmacogenetics of other isoforms, metabolizing enzymes, transferases, transporters, etc, possibly involved in the absorption, distribution, metabolism and excretion of balovaptan and its major metabolites (e.g., CYP3A and P-glycoprotein) may be investigated additionally (e.g. CYP3A5 genotype).

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

Report layout will be according to the PRA EDS – ICH E3 compliant – CSR Template. The layout of TFLs will be according to the PRA EDS standards.

No table shells will be provided. The TFLs will be provided in Adobe PDF format.

Format:

- Page size: A4
- Data in listings will be sorted by subject number and time point.
- Data in tables will be sorted by treatment and time point.
- Column titles will be in title case letters.
- All tables and listings will be in landscape format.
- The treatment labels will be as outlined in Section 9.2.2 Treatment/Subject Grouping Definition

10.0 Analysis Populations

Analyses	Safety	Pharmacokinetic
Disposition Summaries	✓	
Safety Assessments	✓	
Baseline Characteristics	✓	✓
Primary Analysis		✓
PK Concentrations		✓
PK Parameters		✓

10.1 Safety Analysis Population

The safety set will consist of subjects who receive at least one dose of balovaptan. This set will be used for the safety data summaries and baseline characteristic summaries.

10.2 Pharmacokinetic Analysis Population

The PK set will consist of all subjects who receive at least 1 dose of balovaptan. Subject will be excluded from the PK set if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete. Excluded cases will be documented together with the reason for exclusion in the CSR. All decisions on exclusions from the analysis will be made prior to database closure.

11.0 Subject Disposition

The number and percentage of subjects randomized, dosed, and members of each analysis set will be presented. The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented. If the reason for discontinuation is “other”, further specifications will only be listed.

12.0 Protocol Deviations and Violations

Protocol deviations/violations will be included in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

All demographic data as collected during the screenings visit will be listed by subject. Genotype information will be included.

Subject demographics will be summarized descriptively for all subjects by genotype and overall. The summary will include the subjects’ age (in years), gender, race, ethnicity, weight (in kg), height (in cm), and BMI (in kg/m^2). Demographics will be summarized for the safety and (if necessary) for the PK sets.

13.2 Medical History

Medical history will be listed including the coding according to the Medical Dictionary for Regulatory Activities (MedDRA; latest version).

13.3 Other Baseline Characteristics

- Drug and alcohol screen: The results of urine drug screen (barbiturates, benzodiazepines, methadone, amphetamines [including ecstasy], methamphetamines, opiates, cocaine, and cannabinoids and urine alcohol test will be listed.
- Serology: The results of serology (human immunodeficiency virus (HIV)-1 and HIV-2, hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibody) at screening will be listed.
- Pregnancy test (females only): Serum pregnancy test results (beta-human chorionic gonadotropin) and follicle-stimulating hormone (FSH) will be listed for each female subject at screening, each admission to the clinical research center and at follow-up.
- Body weight will be listed at screening and at follow-up.
- Non-compliance to in- or exclusion criteria (if any) will be listed.

14.0 Concomitant Medications

Concomitant medications, categorized by medication group and subgroup according to GNE Drug dictionary, will be summarized. The number and percentage of subjects using each medication will be displayed with the number and percentage of subjects using at least one medication within each medication group and subgroup, by treatment.

Concomitant medication will be listed. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be noted in the listing. If a partial date allows a medication to be considered concomitant it will be categorized as such.

15.0 Treatment Compliance and Exposure

Exposure data will be listed by subject.

The number of subjects receiving each dose of study drug will be summarized.

16.0 Pharmacokinetic Analyses

PK concentrations will be collected in plasma.

16.1 Pharmacokinetic Variables

16.1.1 Concentrations

- Plasma concentration of balovaptan
- Plasma concentration of metabolite M2
- Plasma concentration of metabolite M3
- Plasma concentration of rifampicin

16.1.2 Parameters

- PK Parameters for balovaptan, M2, M3 and rifampicin as defined in Table 1.

Table 1: Plasma Parameters

Parameter	Description	Analyte/ Analysis Day	SAS Programming Notes
C_{max}	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	All analytes/ Analysis Day 10 (or Day 6 for rifampicin)	Cmax from WNL
C_{trough}	Concentration at the end of the dosing interval (tau)	All analytes	The concentration at 24 h calculated in SAS
t_{max}	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	All analytes/ Analysis Day 10 (or Day 6 for rifampicin)	Tmax from WNL
$AUC_{0\text{-last}}$	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	Rifampicin/ Analysis Day 6	AUClast from WNL
$AUC_{0\text{-}24h}$	Area under the serum concentration-time curve from time 0 to 24 hours post-dose	All analytes/ Analysis Day 10 (or 6 for rifampicin)	AUC0-24 from WNL where partial time =24, if missing for a subject then AUC at nominal time 24 hr from summary file is used for AUC0-24
λz	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least three points and an adjusted R^2 greater than 0.70 are required to obtain a reliable λz.	All analytes/ Analysis Day 10 (or 6 for rifampicin)	Lambda_z from WNL If adjusted $R^2 \leq 0.7$ the parameter is not estimated
$t_{1/2}$	Terminal phase half-life expressed in time units. Percent extrapolation <20% and adjusted R^2 greater than 0.7 is required to obtain a reliable $t_{1/2}$.	All analytes/ Analysis Day 10 (or 6 for rifampicin)	HL_Lambda_z from WNL If adjusted $R^2 \leq 0.7$ the parameter is not estimated
MR_C_{max}	Metabolite to parent (balovaptan) ratio of Cmax	M2, M3	Cmax (metabolite)/ Cmax (parent) from WNL *Corrected for molecular weight.
$MR\_AUC_{0\text{-}24h}$	Metabolite to parent (balovaptan) ratio of $AUC_{0\text{-}24h}$	M2, M3	AUC0-24 (metabolite)/ AUC0-24 (parent) from WNL *Corrected for molecular weight.

Note: AUCs will be calculated using linear up / log down, expressed in units of concentration x time.

16.2 Pharmacokinetic Summaries

16.2.1 Pharmacokinetic Concentrations

Plasma concentrations for balovaptan, M2, M3 and rifampicin below the quantifiable limit (BQL) will be set to ½ lower limit of quantification (LLOQ) in the computation of mean concentration values.

Descriptive statistics (number of subjects, arithmetic mean, geometric mean, SD, coefficient of variation, median, min, and max) will be used to summarize the serum concentrations by treatment at each scheduled time point. If over ½ the subjects in a given cell have values BQL then the descriptive statistics will not be presented and will instead display as BQL for the mean and minimum. With the exception of maximum all other statistics will be missing.

Linear and semi-logarithmic plots of the geometric mean plasma concentration by scheduled sampling time will be provided by treatment. These plots will show time in hours. The plots will match the summary table results and will not have an observation at a given time point if more than half of the subjects have values BQL.

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by subject (one subject per page). These plots will show time in hours. Separate plots will be created for the total profile including all analysis periods/treatments and for the Analysis Day 10 time-profiles (balovaptan versus balovaptan + rifampicin) separately. Individual plots will use the BQL handling procedure described below for “Pharmacokinetic Parameters”.

Individual plasma concentration data will be presented together with descriptive statistics by analyte and treatment.

16.2.2 Pharmacokinetic Parameters

PK parameters for balovaptan, M2, M3 and rifampicin will be estimated using non-compartmental methods with WinNonlin®.

The plasma PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters, BQL values will be set to zero for the pre-dose PK sample, as well as for all other samples being BLQ and occurring before t_{max}. For subsequent time points, the result will be set to missing. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter.

Descriptive statistics (number of subjects, arithmetic mean, geometric mean, SD, geometric and arithmetic CV, median, min, and max) will be used to summarize the calculated PK parameters by treatment. For t_{max}, only median, min and max will be presented.

The points to be included in the λz range will be determined by the pharmacokineticist after inspection of the semi-log concentration-time profiles. At least 3 points will be required to be used and the range should ideally be spread over a time interval representing at least 2 half-lives. The C_{max} data point will not be included.
Parameters based on R^2 below 0.70 or $\%AUC_{extra}$ above 20% will be flagged and excluded from descriptive statistics.

16.2.2.1 Drug-Drug Interaction

The effect of rifampicin on the PK of balovaptan will be assessed. The effect of rifampicin on the natural log-transformed C_{max} and $AUC_{0\text{-}24h}$ will be assessed with a linear mixed effects model. Treatment will be fitted as fixed effect and subject as a random effect. Point estimates for the means and point estimates and corresponding 90% CI for the differences in means between the two treatments (balovaptan plus rifampicin as the test treatment, versus balovaptan alone as the reference) will be obtained from the linear mixed effects model and exponentiated to obtain geometric means, geometric mean ratios and respective 90% CI on the original scale.

In addition, as an exploratory analysis CYP3A4 genotype will be added as a factor. The relationship between other genotypes (e.g. CYP3A5) may also be explored.

17.0 Safety Analyses

17.1 Safety Variables

The following safety variables will be summarized:

- Adverse Events (AEs)
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure (SBP)
    - Diastolic Blood Pressure (DBP)
  - Pulse rate
  - Body temperature (tympanic)
  - Respiratory rate
- Electrocardiograms (ECG)
  - Heart Rate
  - PR Interval
  - QRS-Duration
  - QT Interval
  - QTc (Fridericia) Interval
- Clinical Laboratory Evaluations
  - Serum Chemistry
  - Hematology
  - Urinalysis
  - Coagulation
- Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Suicidal ideation
  - Suicidal behavior

17.1.1 Adverse Events

All AEs will be coded to the current version of Medical Dictionary for Regulatory Activities (MedDRA, the latest version) by F. Hoffmann-La Roche, Ltd.

All AE summaries will include only treatment emergent adverse events (TEAEs). Treatment-emergent adverse events are those which occur after the first dose of study drug. AEs starting prior to medication dosing in the first period will be regarded as pre-dose AEs (i.e. non-TEAEs).

TEAEs occurring following dosing in a specific analysis period but before dosing in the next analysis period will be attributed to that specific analysis period, thus to the last received treatment. If the time is missing for an AE on a dosing day then the AE will be attributed to the treatment given on that day.

All adverse events (including non-TEAEs) recorded on the eCRF will be listed (including analysis period and treatment information). Pre-dose AEs will be presented in a separate listing. In addition, a separate listing of AEs leading to withdrawal from study will be provided.

TEAEs will be tabulated by system organ class and preferred term: one table with all TEAEs (number and percentage of subjects) overall and by treatment; one table with related TEAEs (number and percentage of subjects) by treatment; one table with all TEAEs (number and percentage of subjects) by treatment and relationship to study drug; one table with TEAEs (number and percentage of subjects) by treatment and severity.

Subjects are counted once, per preferred term per treatment, for the most severe of multiple occurrences (in case of severity) or most drug-related event (in case of relationship) of a specific MedDRA term. AEs

whose causal relationship was characterized as 'Yes'/'No' will be regarded as being related/not related to the study medication.

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date one minute after dosing
- Missing AE start date will be attributed to the treatment from analysis period 1 unless the AE end date occurs before first IMP administration

17.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events (SAE) will be provided by subject.

17.1.3 Laboratory Data

Clinical laboratory data will be presented using units from the study data tabulation model (SDTM) Controlled Terminology.

All laboratory data will be listed, including laboratory variables not listed in the protocol. A separate listing, including out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology and urinalysis (observed and derived changes from baseline) by treatment and scheduled time will be provided. For categorical urinalysis parameters frequency tables, showing the number of subjects in a category (n) and the percentage of the total number of subjects per treatment (N), will be provided. Sporadic urinalysis tests that were performed when abnormalities were observed (i.e. microscopy/sediment) will only be listed.

17.1.4 Vital Signs

All vital signs data including derived changes from baseline will be listed.

Descriptive statistics will be provided to summarize vital signs including changes from baseline by treatment and scheduled time.

17.1.5 Electrocardiograms

All ECG parameters (including changes from baseline) and the corresponding abnormalities and physician's conclusions will be listed by subject.

The observed measurements for all ECG parameters (including T-wave, U-wave) and the corresponding abnormalities will be listed for all time points. The means of triplicate measurements for continuous parameters and the change from baseline of the mean triplicate measurements at each scheduled time point will be listed by subject.

Descriptive statistics will be provided to summarize mean continuous ECG parameters (observed and changes from baseline) by treatment and scheduled time. A frequency table will be provided as well to summarize the ECG parameters by physicians conclusion (normal, abnormal not clinically significant, abnormal clinically significant).

17.1.6 Columbia Suicide Severity Rating Scale

C-SSRS is a clinical tool used to assess the lifetime suicidality of a subject (C-SSRS lifetime version) as well as any new instances of suicidality (C-SSRS since last visit). It captures the occurrence, severity and

frequency of suicide-related thoughts and behaviors during the assessment period. All individual C-SSRS results will be listed.

18.0 References

1. SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

2. Clinical Study Protocol. A SINGLE-CENTER, NON-RANDOMIZED, OPEN-LABEL, ONE-SEQUENCE, TWO-PERIOD WITHIN-SUBJECT STUDY TO INVESTIGATE THE EFFECTOF RIFAMPICIN ON THE PHARMACOKINETICS OF MULTIPLE DOSES OF BALOVAPTAN IN HEALTHY VOLUNTEERS Version 1.0, Final, 03 Jun 2018.

3. F. Hoffmann-La Roche LTD
CLINICAL PHARMACOLOGY GUIDING PRINCIPLES CALCULATION AND ANALYSES OF NON-COMPARTMENTAL PHARMACOKINETIC PARAMETERS Version 4.0, Jul 2015

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ADAE	Adverse Event Analysis Dataset
ADaM	Analysis data model
ADPC	PK Concentrations Analysis Dataset
ADPP	PK Parameters Analysis Dataset
ADSL	Subject Level Analysis Dataset
BMI	Body mass index
BQL	Below the quantifiable limit
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CRU	Clinical research unit
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical study report
CV	Coefficient of variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
FSH	Follicle-stimulating hormone
HIV	Human immunodeficiency virus
HBsAg	Hepatitis B virus surface antigen

HCV	Hepatitis C virus
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
M2, M3	Metabolites
PK	Pharmacokinetic
QA'd	Quality assured
QC'd	Quality controlled
qd	Once daily
SAP	Statistical analysis plan
SAE	Serious adverse event
SBP	Systolic Blood Pressure
SD	Standard deviation
SDTM	Study data tabulation model
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
WNL	WinNonlin

Appendix 2: Schedule of Assessments

				Washout of minimally 14 and maximally 21 days between the study periods										
Assessments	**Screening**		**Period 1**				**Period 2**							**Follow-up**
	Day -21 to Day -2	Day -1	Days 1-9	Day 10	Day 11	Washout: for 14-21 days after last dose	Day -1	Days 1-5	Day 6	Day 7	Days 8-15	Day 16	Day 17	Days 30 – 37 of Period 2
Written informed consent	X													
Inclusion and exclusion criteria	X													
Demographics	X													
Medical history	X													
Medication history	X													
Study drug administration: balovaptan[a]			X	X						X	X	X		
Study drug administration: rifampicin[a]								X	X	X	X	X		
Standardized meals[b]				X					X			X		
Pharmacokinetic sampling balovaptan[c]			X	X	X						X	X	X	
Clinical genotyping sample		X												
Pharmacokinetic sampling rifampicin[d]									X	X		X	X	
Physical examination	X[e]				X		X[f]						X	X[f]
Triplicate 12-lead ECG[g]	X	X	X	X	X		X	X	X	X	X	X	X	X
Vital signs[h]	X[i]	X[i]	X	X[i]	X[i]		X[i]		X[i]	X	X	X[i]	X[i]	X[i]
Hematology[j]	X	X			X		X	X	X	X	X		X	X
Serum chemistry[j]	X	X			X		X	X	X	X	X		X	X
Urinalysis[j]	X	X			X		X						X	X
Coagulation	X						X							
Urine drug screen	X	X					X							
Urine alcohol test	X	X					X							
Serology	X													
Pregnancy test[k]	X	X					X							X
Resident at study center[l]		X	X	X	X		X	X	X	X	X	X	X	
Adverse event monitoring	X	←	—	—	→		←	—	—	—	—	—	→	X
Review concomitant medications	X	←	—	—	→		←	—	—	—	—	—	→	X
C-SSRS	X				X								X	

Abbreviations: BMI = body mass index; C-SSRS= Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; qd = once daily;

a Study drugs will be administered after an overnight fast of at least 8 hours, 30 minutes prior to breakfast. On days rifampicin and balovaptan are coadministered, they will be administered at the same time. Water will be allowed ad libitum up to 1 hour prior to dosing and from 1 hour post dosing, and no food is allowed for at least 4 hours post dose—lunch, dinner, and afternoon/ evening snacks will be provided 4 or more hours after dosing.

b A standardized breakfast will be provided at least 30 minutes after dosing of balovaptan alone, rifampicin alone, or balovaptan + rifampicin together in either period. A standardized lunch and standardized dinner will be provided 4 and 10 hours post dose, respectively, in both periods. Standardized afternoon and evening snacks will be provided as well.

c Samples to measure the concentration of balovaptan, M2, and M3 (one sample per time point to measure all 3 analytes) will be taken at predose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, hours post dose on Days 10/11 of Period 1 (16- and 24-hour samples are on the morning of Day 11) and 16/17 of Period 2 (16- and 24-hour samples are on the morning of Day 17). A predose sample to measure the concentration of balovaptan, M2, and M3 will also be taken on Days 2, 4, 8, and 9 in Period 1, and on Days 8, 10, 14, and 15 in Period 2 (see also Appendix 2).

d Samples to measure the concentration of rifampicin will be taken predose and at 1, 1.5, 2, 3, 4, 6, 12, and 24 hours post dose of rifampicin on Days 6/7 and 16/17 of Period 2 (24-hour samples are on the morning of Days 7 and 17) (see also Appendix 2).

e Includes measurement of height, weight and BMI.

f Includes measurement of weight.

g Triplicate ECGs will be collected as follows: in Period 1, on Day -1 and predose and 3 hours after dosing of balovaptan on Days 3, 7, and 10 and in the morning of Day 11; and in Period 2, on Day -1, and predose and 3 hours post dose on Days 3, 6, 9, 13, and 16; in the morning of Day 17, and at Follow-up (see also Appendix 2).

h Vital signs will be collected as follows: in Period 1, on Day -1 and predose and 3 hours after dosing of balovaptan on Days 3, 7, and 10 and in the morning of Day 11; and in Period 2, on Day -1, and predose and 3 hours post dose on Days 3, 6, 9, 13, and 16; in the morning of Day 17, and at Follow-up (see also Appendix 2).

i Includes measurement of body temperature.

j Hematology and chemistry at Screening and on Days -1 and 11 of Period 1 and on Days -1, 3, 6, 9, 13, 17 in Period 2, and follow up. Urinalysis at Screening and on Days -1 and 11 of Period 1 and on Days -1 and 17 in Period 2 and at Follow-up.

k For females only: FSH and serum pregnancy test at Screening, and serum pregnancy test only at all other time points.

l Subjects will be admitted to the clinical research unit on Day -1 of Period 1 and Period 2 and will be discharged on Day 11 and Day 17 of Period 1 and 2, respectively, after completion of study assessments.

Appendix 3: Schedule of PK, ECG and VS Measurements

Procedure Study Day	Predose or Prior to Admission/Discharge	Hours post dose[a]											
		0.5	1	1.5	2	2.5	3	4	6	8	12	16	24
Blood sampling balovaptan, M2, and M3 (one sample for all 3 analytes)													
Period 1													
Days 2, 4, 8, and 9	X[b]												
Day 10	X[b]	X	X	X	X	X	X	X	X	X	X	X[c]	X[c]
Period 2													
Days 8, 10, 14, and 15	X[b]												
Day 16	X[b]	X	X	X	X	X	X	X	X	X	X	X[d]	X[d]
Blood sampling rifampicin													
Period 2													
Day 6	X[b]		X	X	X		X	X	X		X		X[e]
Day 16	X[b]		X	X	X		X	X	X		X		X[d]
12-lead electrocardiograms													
Period 1													
Day -1 and Day 11	X[f]												
Days 3, 7, and 10	X[b]						X						
Period 2													
Day -1 and Day 17	X[f]												
Days 3, 6, 9, 13, and 16	X[b]						X						
Vital signs													
Period 1													
Day -1 and Day 11	X[f]												
Days 3, 7, and 10	X[b]						X						
Period 2													
Day -1 and Day 17	X[f]												
Days 3, 6, 9, 13, and 16	X[b]						X						

[a]For sampling to measure balovaptan, M2, and M3, and for ECG and vital signs measurements on days balovaptan or balovaptan together with rifampicin are administered, post dose is relative to time of balovaptan dosing; for sampling to measure rifampicin and for ECG and vital signs measurements on days balovaptan is not administered, post dose is relative to time of rifampicin dosing
[b]10 minutes predose (or time matched, when not dosed)
[c]Day 11
[d]Day 17
[e]Day 7
[f]Prior to admission or discharge

Appendix 4: List of End of Text Outputs

List of End of Text Tables and Figures:		
Output	**Title**	**Population Set**
Section 14.1 – Disposition and Demographic Data		
Table 14.1.1	Summary of Subject Disposition	Safety
Table 14.1.2.1	Summary of Demographics	Safety
Table 14.1.2.2	Summary of Demographics (if applicable)	PK
Section 14.2 – Pharmacokinetic Data		
Table 14.2.1	Individual Values and Descriptive Statistics of Balovaptan Plasma Concentrations	PK
Table 14.2.2	Individual Values and Descriptive Statistics of Balovaptan Plasma Parameters	PK
Table 14.2.3	Individual Values and Descriptive Statistics of Balovaptan Metabolite (M2, M3) Plasma Concentrations	PK
Table 14.2.4	Individual Values and Descriptive Statistics of Balovaptan Metabolite (M2, M3) Plasma Parameters	PK
Table 14.2.5	Individual Values and Descriptive Statistics of Rifampicin Plasma Concentrations	PK
Table 14.2.6	Individual Values and Descriptive Statistics of Rifampicin Plasma Parameters	PK
Table 14.2.7	Statistical Analysis of the effect of Rifampicin on Balovaptan	PK
Figure 14.2.8.1	Geometric Mean Balovaptan Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.8.2	Geometric Mean Balovaptan Metabolite (M2, M3) Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.8.3	Geometric Mean Rifampicin Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.9.1	Total Profile of Individual Balovaptan Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.9.2	Total Profile of Individual Balovaptan Metabolite (M2, M3) Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	Safety

Figure 14.2.9.3	Total Profile of Individual Rifampicin Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.9.4	Combined Total profile of Individual Balovaptan Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.9.5	Combined Total profile of Individual Balovaptan Metabolite (M2, M3) Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.9.6	Combined Individual Rifampicin Plasma Concentrations versus Time (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.9.7	Individual Balovaptan Plasma Concentrations versus Time – Analysis Day 10 (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.9.8	Individual Balovaptan Metabolite (M2, M3) Plasma Concentrations versus Time – Analysis Day 10 (Linear and Semi-Logarithmic Scale)	Safety
Section 14.3 – Safety Data		
Section 14.3.1 Adverse Events		
Table 14.3.1.1	Summary of TEAEs for Each System Organ Class and Preferred Term (Number and Percentage of Subjects) by Treatment	Safety
Table 14.3.1.2	Summary of Related TEAEs for Each System Organ Class and Preferred Term (Number and Percentage of Subjects) by Treatment	Safety
Table 14.3.1.3	Summary of TEAEs for Each System Organ Class and Preferred Term (Number and Percentage of Subjects) by Treatment and Relationship to Study Drug	Safety
Table 14.3.1.4	Summary of TEAEs for Each System Organ Class and Preferred Term (Number and Percentage of Subjects) by Treatment and Severity	Safety
Section 14.3.2 Lists of Deaths, Other Serious and Significant Adverse Events		
Table 14.3.2.1	Listing of Deaths and Other Serious Adverse Events	Safety
Section 14.3.3 Clinical Laboratory		
Table 14.3.3.1	Listing of Abnormal Laboratory Values	Safety
Table 14.3.3.2	Descriptive Statistics of Clinical Laboratory Results - Hematology	Safety
Table 14.3.3.3	Descriptive Statistics of Clinical Laboratory Results – Serum Chemistry	Safety
Table 14.3.3.4	Descriptive Statistics of Clinical Laboratory Results - Urinalysis	Safety
Section 14.3.4 Other Safety		
Table 14.3.4.1	Descriptive Statistics of Vital Signs	Safety
Table 14.3.4.2	Summary of 12-Lead Electrocardiogram	Safety
Table 14.3.4.3	Frequency of 12-Lead Electrocardiogram Physicians Conclusion	Safety

Table 14.1.4.4	Summary of Treatment Compliance	Safety

List of End of Text Listings:	
Output	**Title**
Section 16.2.1 – Disposition	
Listing 16.2.1	Subject Disposition
Section 16.2.2 – Protocol Deviations	
	Not part of TFL – Reserved for protocol deviations in CSR
Section 16.2.3 – Excluded Subjects	
Listing 16.2.3.1	Analysis Sets
Section 16.2.4 – Demographics and Baseline Characteristics	
Listing 16.2.4.1	Subject Demographics (including genotype)
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Prior and Concomitant Medications
Listing 16.2.4.4	Drug and Alcohol Screen
Listing 16.2.4.5	Serology Test Results
Listing 16.2.4.6	Pregnancy and Serum FSH Test Results
Listing 16.2.4.7	Genotyping Results
Section 16.2.5 – Compliance and Drug Concentration Data	
Listing 16.2.5.1	Study Dates
Listing 16.2.5.2	Study Drug Administration
Listing 16.2.5.3	Deviations from Inclusion/Exclusion criteria
Listing 16.2.5.4	PK Blood Sampling Time Deviations and Comments
Listing 16.2.5.5	Food Intake
Section 16.2.7 – Adverse Events Data	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading to Withdrawal
Section 16.2.8 – Laboratory Data	
Listing 16.2.8.1	Clinical Laboratory Results – Hematology
Listing 16.2.8.2	Clinical Laboratory Results – Chemistry
Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis
Listing 16.2.8.4	Clinical Laboratory Results – Coagulation
Section 16.2.9 – Other Safety Data	
Listing 16.2.9.1	Vital Sign Results
Listing 16.2.9.2	12-Lead Electrocardiogram Results

Listing 16.2.9.3	Abnormalities and Changes in Findings at the Physical Examinations
Listing 16.2.9.4	Columbia-Suicide Severity Rating Scale

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.7	Randomization
Appendix 16.1.9.2	Statistical Appendices

Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
04-Oct-2018	[redacted]	Comments from 3rd sponsor review
14-Sep-2018	[redacted]	Comments from 2nd sponsor review
06-Aug-2018	[redacted]	Comments from sponsor review
16-Jul-2018	[redacted]	Comments from internal review (MW/BS)
11-Jul-2018	[redacted]	Created first draft from Template