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

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Statistical Analysis Plan

Sponsor:	F. Hoffmann-La Roche Ltd
Protocol No	WP40609
Protocol Title:	A SINGLE-CENTER, NON-RANDOMIZED, OPEN-LABEL, ONE-SEQUENCE, TWO-PERIOD WITHIN-SUBJECT STUDY TO INVESTIGATE THE EFFECT OF ITRACONAZOLE ON THE PHARMACOKINETICS OF MULTIPLE DOSES OF BALOVAPTAN IN HEALTHY VOLUNTEERS
PRA Project ID	RPU035EC-180351
Version Date	14-Nov-2018

1.0 Approvals

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

Representatiye >: Title: . .	[redacted], Biostatistician
Signature of Sponsor Representative / Date	[redacted] A6-- Abv '6J).t
Name of Author/ Title:	[redacted], Principal Biostatistician
Signature of Author / Date	[redacted] Signed by: [redacted] Principal Biostatistician Reason: I am the author of this document Date & Time: 20 Nov 2018 02:34 PM +01:00

Pharmaceutical Research Associates Group BV , a PRA Health Sciences company

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 WP40609.

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 protocol Version 1.0 dated 18-May-2018 [2] and the final eCRF(s) dated 05-Jul-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 itraconazole treatment on the PK of balovaptan and its major metabolites M2 (RO7045402) and M3 (RO5273004).

5.1 Primary Objective

To investigate the effect of itraconazole treatment on the PK of balovaptan and its major metabolites M2 (as applicable) and M3, at steady state.

5.1.1 Primary PK Endpoints

PK parameters for balovaptan, M2, and M3 after 15 days of balovaptan qd dosing in Period 2, and after 10 days of balovaptan qd dosing in Period 1:

- Maximum observed plasma concentration (C_{max})
- Area under the concentration vs time curve (AUC) over the dosing interval ($AUC_{0-\tau}$)

5.1.2 Additional PK Endpoints

Additional PK endpoints: balovaptan, M2, and M3 time to maximum observed plasma concentration (T_{max}), trough plasma concentration (C_{trough}), and time to steady state

5.2 Secondary Objective

To explore the safety and tolerability of balovaptan when given alone and in combination with itraconazole in healthy subjects.

5.2.1 Secondary Endpoints

- Adverse events (AEs),

- clinical laboratory values,
- vital signs,
- electrocardiogram (ECG), and
- physical examination.

5.3 Tertiary/Exploratory Objectives

- Relationship between the CYP3A4 genotype, among others, and steady state balovaptan exposure, and the influence of the CYP3A4 genotype, among others, on the effect of itraconazole on balovaptan PK
- The plasma exposure of itraconazole and hydroxy (OH)-itraconazole

5.3.1 Tertiary/Exploratory Endpoints

- The pharmacogenetics of metabolizing enzyme, transferases, transporters, etc, possibly involved in the absorption, distribution, metabolism, and excretion of balovaptan and its major metabolites (eg, CYP3A4 and P-glycoprotein). Note that results may be pooled with data from other studies of balovaptan, but the results of such pooling will not be included in the CSR for this study.
- Area under the curve from time 0 to 24 hours ($AUC_{0\text{-}24h}$), C_{max}, and T_{max} on Day 5 and Day 20

6.0 Study Design

This study will be non-randomized, open-label, one-sequence, two-period within-subject study to investigate the effect of CYP3A inhibition on the PK of balovaptan in healthy male and female volunteers using itraconazole as a CYP3A inhibitor. The study will be conducted at 1 site in the Netherlands.

Subjects will be screened for eligibility for the study for up to 28 days before the first dose of study drug. In Period 1, eligible subjects will be admitted to the clinical research unit (CRU) in the afternoon of Day -1 and remain in the CRU until discharge in the morning of Day 11. There will be at least a 7-day washout between the last dose in Period 1 and the first dose in Period 2. After this washout period, subjects will return to the CRU on Day -1 of Period 2 and remain in the CRU until discharge on Day 21 of Period 2. For each study period, dosing will begin on Day 1. Subjects will receive the following study drugs in 2 periods over a total of 37 days:

Period 1:

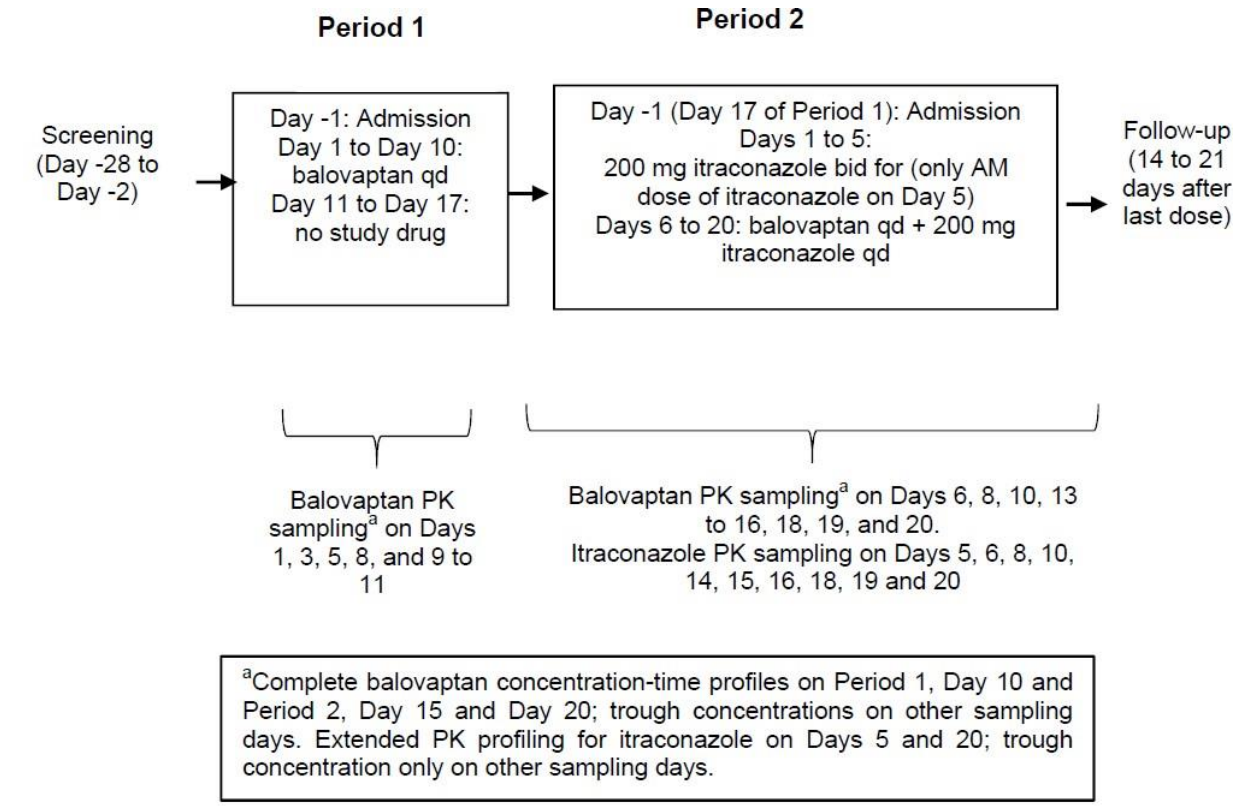
- Days 1 to 10: oral balovaptan once daily (qd)
- Days 11 to 17: no study drug

Period 2:

- Days 1 to 5: 200 mg itraconazole twice daily, approximately 12 hours apart (on Day 5, only the AM dose of itraconazole will be administered)
- Days 6 to 20: balovaptan qd + 200 mg itraconazole qd

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 2.

Figure 1 Study Schema



Abbreviations: bid = twice daily; PK = pharmacokinetics; qd = once daily

On Period 1 Day 10 and Period 2 Day 20, balovaptan will be dosed at the same time of day. On Period 2 Days 5 and 20 itraconazole will be dosed at the same time of day. On Period 2 Days 6 to 20, itraconazole will be administered in combination with balovaptan.

Subjects will undergo study assessments and procedures, including assessments of AEs and concomitant medications, vital signs, 12-lead ECGs, clinical laboratory evaluations and blood sampling for PK assessments and genotyping as per the schedule of assessments in Appendix 3.

The dose of balovaptan to be used during balovaptan alone and balovaptan plus itraconazole dosing periods will be 5 mg qd for an initial sentinel cohort of 4 subjects (Cohort A). The safety, tolerability, and PK data up to 24 hours after the final dose of balovaptan (when given in conjunction with itraconazole), for at least 3 of the 4 subjects, will be reviewed by the by the Sponsor's Medical Monitor or designee and the Investigator. There will be at least a 20-day period between Cohort A and Cohort B to allow for analysis of PK data. After review of the data, a dose of balovaptan will be selected for the remainder of subjects (Cohort B). The dose may remain 5 mg qd or may be increased to 10 mg qd, depending on data from Cohort A. The dose may be increased to 10 mg qd for Cohort B if the highest mean exposure values for C_{max} and $AUC_{0\text{-}tau}$ in the presence of itraconazole in Cohort A and the projected exposures expected for Cohort B do not exceed the highest exposures seen with multiple dosing of balovaptan 52 mg (484 ± 43.1 ng/mL for C_{max} and 5920 ± 817 h·ng/mL for $AUC_{0\text{-}tau}$) and there are no prohibitive safety findings based on a review of safety data from Cohort A. If these criteria are not met, dosing will be continued at 5 mg qd in Cohort B.

If a decision is made to keep the dose at 5 mg qd, a total of 10 subjects will enter Cohort B. If a decision is made to increase the dose to 10 mg qd, a total of 14 subjects will enter Cohort B.

6.1 Sample Size Considerations

This is an exploratory study for which no formal statistical hypothesis will be tested, and therefore the sample size is chosen to estimate, with sufficient precision, the CYP3A4 inhibition on balovaptan. Between 14 and 18 subjects will be enrolled, so as to have 14 subjects enrolled on either 5 mg or 10 mg balovaptan to ensure a minimum of 12 completers. The sample size was chosen based on balovaptan within-subject variability (CV%) of around 39% for AUC0-τ 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% CI for the ratio of treatment geometric means of the combination (balovaptan + itraconazole) versus balovaptan alone would be obtained by dividing/multiplying the ratio estimate by a factor of 1.30

6.2 Randomization

This study is not randomized. All subjects will receive the same treatment sequence.

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

Interim PK analyses, including the calculation of the PK parameters for both periods, will be done for Cohort A. The data from this analysis will be used in the decision whether the balovaptan dose should be increased from 5 to 10 mg qd for Cohort B.

For the interim analysis and reporting a separate plan was written.

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 and transfer 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 and geometric mean values with 1 more decimal digit, standard deviation (SD) with 2 more decimal digits. Percentages will be rounded to integers.

For descriptive statistics of PK parameters, precision and significant figures as described in Appendix 2 of the Roche PK NCA guideline, see [4], will be used. 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).

In case the dose for Cohort B is not increased from 5 to 10 mg, the data from Cohorts A and B will be pooled. In case the dose for Cohort B is increased from 5 to 10 mg, the data from Cohort A will be not be pooled but rather reported separately.

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 study 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 Period 1.

9.2.2 Treatment/Subject Grouping

In the analyses, analysis period will be used as opposed to the study period as defined in the protocol (see also Section 6.0). This means that Study Period 2 will be divided in two analysis periods, Period 2 (Study Days -1 to 5) and Period 3 (Study Days 6 to 21). The study will therefore consist of 3 analysis periods as shown in Table 1.

Table 1 Analysis Periods

Study Period	Analysis Period	Study Day	Analysis Day	Treatment
1	1	-1 to 11	-1 to 11	Analysis Day 1-10: oral balovaptan once daily (qd)
2	2	-1 to 5	-1 to 5	Analysis Day 1-5: 200 mg itraconazole twice daily (bid) approximately 12 hours apart (on Analysis Day 5, only the AM dose of itraconazole will be administered)
2	3	6 to 21	1 to 16	Analysis Days 1-15: balovaptan qd + 200 mg itraconazole qd

Analysis Period 1 starts 1 day before dosing with balovaptan alone and ends 1 day before dosing with itraconazole (the washout of at least 7 days will be included in this analysis period). Analysis Period 2 starts 1 day before dosing with balovaptan alone and ends 1 day before dosing with itraconazole (the washout of at least 7 days will be included in this analysis period).

Analysis Period 2 starts 1 day before dosing with itraconazole alone and ends just before dosing with balovaptan and itraconazole on Study Day 6.

Analysis Period 3 starts just before dosing with balovaptan and itraconazole on Study Day 6 and ends with start of Follow-up visit (14 to 21 days post-dose). Any pre-dose assessments planned on the first day of dosing with balovaptan and itraconazole will belong to this Analysis Period.

Depending on the outcome of the interim analysis after Cohort A and the subsequent decision whether the balovaptan dose should be increased from 5 to 10 mg qd for Cohort B, there will be either 3 or 5 different treatments in this study.

Table 2 Treatments

Treatment #	Treatment Label	Treatment Description
1	5 mg balovaptan (S)	5 mg oral balovaptan once daily (qd) on Analysis Day 1 to 10 of Analysis Period 1 (Cohort A and possibly Cohort B)
2	200 mg itraconazole (I)	200 mg itraconazole twice daily (bid) on Analysis Day 1-4 and morning dose on Analysis Day 5
3	5 mg balovaptan + 200 mg itraconazole (S+I)	5 mg balovaptan qd + 200 mg itraconazole qd on Analysis Days 1-15 of Analysis Period 3 (Cohort A and possibly Cohort B)
4*	10 mg balovaptan (S)	10 mg oral balovaptan once daily (qd) on Analysis Day 1 to 10 of Analysis Period 1 (Cohort B in case of dose increase)
5*	10 mg balovaptan + 200 mg itraconazole (S+I)	5 mg balovaptan qd + 200 mg itraconazole qd on Analysis Days 1-15 of Analysis Period 3 (Cohort B in case of dose increase)
*) These treatments will only be included if it was decided to increase the balovaptan dose from 5 to 10 mg for Cohort B S = Substrate, I = Index Inhibitor		

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation	Note
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.	ADaM variable APERIOD
Change from Baseline	All	Post-dose Observation minus Baseline Observation	ADaM variable CHG
Analysis Day	All	For pre-dose days: date of assessment minus (first) dose date in each analysis period. For post dose days: Date of assessment minus (first) dose date in each analysis period +1	ADaM variable ADY

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 (Pharsight, Inc.). 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, see also Section 16.2.2.1.

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., CYP3A4 and P-glycoprotein) may be investigated additionally.

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

10.1 Safety Analysis Population

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

10.2 Pharmacokinetic Analysis Population

The PK analysis population will consist of all subjects who receive at least 1 dose of balovaptan. Subjects will be excluded from the PK analysis population 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 in the CSR together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

In case the dose for Cohort B was increased from to 10 mg balovaptan, Subjects from Cohort A will be excluded from the PK analysis population.

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 analysis set.

13.2 Medical History

Medical history will be listed including the coding according to the and coded using 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 M2 (as applicable)
- Plasma concentrations of M3
- Plasma concentrations of itraconazole
- Plasma concentrations of OH-itraconazole

In Analysis Period 1, pre-dose (trough) balovaptan, M2 and M3 concentrations will be measured on Analysis Days 1, 3, 5, 8 and 9. A full PK profile of balovaptan, M2 and M3 concentrations will be measured on Analysis Day 10: pre-dose (0), 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24h (where these last samples will actually be taken on Analysis Day 11, but as they are related to the dosing on Day 10, will considered to belong the Day 10 profile).

In Analysis Period 2, itraconazole and OH-itraconazole concentrations will be measured on Analysis Days 5: pre-dose (0), 2, 4, and 8h. The pre-dose sample taken on Analysis Day 1 of Analysis Period 3 can considered to be the 24h sample for Analysis Day 5 of Analysis Period 2.

In Analysis Period 3, pre-dose (trough) balovaptan, M2 and M3 concentrations will be measured on Analysis Days 1, 3, 5, 8, 9, 10, 11, 13, 14, 15 and 16. A full PK profile of balovaptan, M2 and M3 concentrations will be measured on Analysis Days 10 and 15: pre-dose (0), 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24h (where these last samples will actually be taken on Analysis Day 11 or 16 respectively, but as they are related to the dosing on Day 10 or 15, will considered to belong the Day 10 or 15 profile, respectively). Note that the 24h sample can also be considered the trough concentration on Day 11 or 15.

In Analysis Period 3, pre-dose (trough) itraconazole and OH-itraconazole concentrations will be measured on Analysis Days 1, 3, 5, 9, (11), 13, and 14. Itraconazole and OH-itraconazole concentrations will be also measured on Analysis Days 10 and 15: pre-dose (0), 2, 4, 8h and 24h (where this last sample will actually be taken on Analysis Day 11 or 16 respectively, but as it is related to the dosing on Day 10 or 15, will considered to belong the Day 10 or 15 profile, respectively). Note that the 24h sample can also be considered the trough concentration on Day 11 or 15.

16.1.2 Parameters

- PK Parameters for balovaptan, M2, M3, as defined in Table 1.
- PK Parameters for itraconazole and OH-itraconazole, as defined in Table 1., if feasible.

Table 3 PK Parameter Definitions

Parameter	Description	Balovatan, M2 and M3			itraconazole and OH-itraconazole		SAS Programming Notes
		Analysis Period 1	Analysis Period 3		Analysis Period 2	Analysis Period 3	
		Day 10	Day 10	Day 15	Day 5	Day 15	
C_{max}	Maximum plasma concentration: observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	✓	✓	✓	✓	✓	Cmax from WNL
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.	✓	✓	✓	✓	✓	Tmax from WNL
$AUC_{0\text{-}tau}$	Area under the concentration-time curve over the dosing interval (time 0 to 24hr).	✓	✓	✓			AUCtau from WNL where tau is equal to 24hr
$AUC_{0\text{-}24h}$	Partial area under the concentration-time curve over the 0 to 24hr				✓	✓	AUC0_24 from WNL where partial time =24

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, itraconazole and OH- itraconazole 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, SD, coefficient of variation [CV%], median, min, and max, geometric mean and geometric CV%) 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. Except for the maximum, all other statistics will be missing. Descriptive statistics will be presented together with individual plasma concentration data by analyte, treatment, analysis day and time-point.

Linear and semi-logarithmic plots of the geometric mean balovaptan, M2 and M3 plasma concentrations versus scheduled sampling time will be provided by treatment and analysis day (balovaptan alone on Day 10 and balovaptan + itraconazole on Day 10 and 15). 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 geometric mean itraconazole and OH-itraconazole plasma concentrations versus scheduled sampling time will be provided by treatment and analysis day (itraconazole alone on Day 5 and balovaptan + itraconazole on Day 15). 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.

Combined individual (spaghetti) plots of the individual plasma balovaptan, M2 and M3 plasma concentration versus actual sampling time will be provided by treatment and analysis day (balovaptan alone on Day 10 and balovaptan + itraconazole on Day 10 and 15). These plots will show time in hours.

Combined individual (spaghetti) plots of the individual plasma itraconazole and OH-itraconazole plasma concentration versus actual sampling time will be provided by treatment and analysis day (itraconazole alone on Day 5 and balovaptan + itraconazole on Day 15). These plots will show time in hours.

Linear and semi-logarithmic plots of the individual plasma balovaptan, M2 and M3 plasma concentration by actual sampling time will be provided by subject and treatment (balovaptan alone on Day 1-10 and balovaptan + itraconazole on Days 1-15 These plots will show time in days.

Linear and semi-logarithmic plots of the individual plasma itraconazole and OH-itraconazole concentration by actual sampling time will be provided by subject (balovaptan + itraconazole treatment on Days 1-15 These plots will show time in days.

Linear and semi-logarithmic plots of the geometric mean trough balovaptan, M2 and M3 plasma concentrations versus day will be provided by treatment (balovaptan alone on Days 1-10 and balovaptan + itraconazole on Days 1-16). These plots will show time in Days. The plots will match the summary table results and will not have an observation at a given day if more than half of the subjects have values BQL.

Individual plots will use the BQL handling procedure described below for “Pharmacokinetic Parameters”.

16.2.2 Pharmacokinetic Parameters

PK parameters for balovaptan, M2, and M3 and 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, SD, (arithmetic) CV%, median, min, max, geometric mean and geometric CV%) will be used to summarize the calculated PK parameters by treatment. For T_{max}, only median, min and max will be presented.

16.2.2.1 Drug-Drug Interaction

The effect of itraconazole on the PK of balovaptan on Analysis Days 10 and 15 will be assessed. A linear mixed effect model will used to analyze the natural log-transformed C_{max} and $AUC_{0\text{-}tau}$ values of balovaptan, M2 and M3. An analysis variable representing the combination of treatment and analysis day (balovaptan alone on Day 10, balovaptan + itraconazole on Day 10, and balovaptan + itraconazole on Day 15) will be used as fixed effect and subject will be used as a random effect. The estimates for the differences between

1) balovaptan + itraconazole on Day 15 (test) and balovaptan alone on Day 10 (reference)
2) balovaptan + itraconazole on Day 10 (test) and balovaptan alone on Day 10 (reference)

will be back-transformed to derive the geometric mean ratios of balovaptan + itraconazole (on Days 10 and 15) over balovaptan alone on Day 10 together with the corresponding 90% CIs for the comparisons of the PK parameters.

In addition, as an exploratory analysis, the CYP3A4 genotype will be added as a factor. The relationship between other genotypes 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 treatment received. 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. 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.

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. Physicians conclusion (normal /abnormal not clinically significant/abnormal clinically significant) will be summarized in a frequency table.

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.

17.1.7 Other Observations Related to Safety

Abnormalities and changes in findings at the physical examinations 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 EFFECT OF ITRACONAZOLE ON THE PHARMACOKINETICS OF MULTIPLE DOSES OF BALOVAPTAN IN HEALTHY VOLUNTEERS. Version 1.0, Final, 18-May-2018
3. Interim Analysis Plan A SINGLE-CENTER, NON-RANDOMIZED, OPEN-LABEL, ONE-SEQUENCE, TWO-PERIOD WITHIN-SUBJECT STUDY TO INVESTIGATE THE EFFECT OF ITRACONAZOLE ON THE PHARMACOKINETICS OF MULTIPLE DOSES OF BALOVAPTAN IN HEALTHY VOLUNTEERS, Final Version 1.0, 05-Jul-2018.
4. F. Hoffmann-La Roche Ltd. CLINICAL PHARMACOLOGY GUIDING PRINCIPLES CALCULATION AND ANALYSES OF NON-COMPARTMENTAL PHARMACOKINETIC PARAMETERS, Version 4.0, July 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

		Period 1							Period 2															Follow-up
Procedures	Screening	-1	1	2 to 8	9	10	11	washout (at least 7 days)	-1	1	2	3	4	5	6 to 11	12	13	14	15	16	17 to 19	20	21	14 to 21 days postdose
Informed consent	X																							
Inclusion and exclusion criteria	X	X																						
Demographic data	X																							
Medical history	X	X																						
Urine drug screen and urine alcohol test	X	X							X															
Urinalysis	X	X												X								X	X
Serology	X																							
Coagulation[a]	X																							
Pregnancy test[b]	X	X							X															X
Balovaptan administration[c]			X	X	X	X									X	X	X	X	X	X	X	X		
PK sampling for Balovaptan and metabolites M2 and M3[d]			X	X	X	X	X								X		X	X	X	X	X	X		
Itraconazole administration[e]										X	X	X	X	X	X	X	X	X	X	X	X	X		
PK sampling for Itraconazole and hydroxyl-itraconazole[f]														X	X[n]						X	X		
Genotyping sample		X																						
Physical examination	X								X														X[g]	X
Height, body weight and BMI[h]	X	X							X															

Procedures	Screening	Period 1							Period 2														Follow-up
		-1	1	2 to 8	9	10	11	washout (at least 7 days)	-1	1	2	3	4	5	6 to 11	12	13	14	15	16	17 to 19	20	21	14 to 21 days postdose
Triplicate 12-lead ECG[i]	X	X	X			X				X				X	X[n]		X		X		X[o]	X		X
Vital signs[j]	X		X				X			X					X[n]		X		X		X[o]		X	X
Orthostatic challenge testing	X				X[p]				X				X[p]							X[p]				
Clinical laboratory (hematology, and clinical chemistry)[k]	X	X				X			X			X			X[n]	X			X		X[o]		X	X
Admission		X							X															
Residential stay		X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Discharge							X																X	
Ambulatory visit	X																							X
Standardized meal[l]						X								X					X			X		
C-SSRS[m]	X					X								X								X		
Adverse event monitoring	X	←																			→			X
Review concomitant medications	X	←																			→			X

Abbreviations: BMI = body mass index; C-SSRS= Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; PK = pharmacokinetic;

[a]Prothrombin time (international normalized ratio) and activated partial thromboplastin test only.
[b]Follicle-stimulating hormone test and beta-human chorionic gonadotropin (serum pregnancy test) at screening in all females. At subsequent visits, serum pregnancy test will be performed in all females.
[c]Once daily dosing with food on Period 1, Days 1 to 10 and Period 2, Days 6 to 15, administered in the clinical research unit in the morning between 07:00 and 10:00 AM. On Period 1, Day 10 and Period 2, Day 20, balovaptan will be dosed at the same time of each day.
[d]PK sampling on Days 1, 3, 5, 8, 9, 10, and 11 of Period 1, and on Days 6, 8, 10, 13, 14, 15, 16, 18, 19, and 20 of Period 2. See Appendix 2 for specific PK blood sampling time points for each study day
[e]Dose with food. Twice daily dosing on Days 1 to 4, Period 2, Days 1 to 4. Once daily dosing on Period 2, Days 6 to 20 in combination with balovaptan. On Period 2, Days 5 and 20, itraconazole will be dosed at the same time on each day.
[f]PK sampling on Days 5, 6, 8, 10, 14, 15, 16, 18, 19, and 20 of Period 2. See Appendix 2 for specific PK blood sampling time points for each study day.
[g]Prior to discharge.
[h]Height, weight, and BMI at Screening; weight only on Day -1 of Periods 1 and 2.

[i] See Appendix 2 for specific ECG time points by study day
[j] See Appendix 2 for specific vital signs time points by study day
[k] Prior to breakfast
[l] At predose (breakfast will be provided 30 minutes before dosing and completed within approximately 15 minutes prior to balovaptan or itraconazole dosing), and at 5, 9, and 11.5 hours post dose
[m] Predose
[n] Assessments performed on Days 6, 8, and 10
[o] Assessments performed on Day 17
[p] Test performed about 3 hours after the morning dose of balovaptan. On Day 4 in Period 2, when only itraconazole is dosed, the timing of the orthostatic challenge test should correspond to 3 hours after the time of balovaptan dosing in Period 2.

Appendix 3: Schedule of PK Sampling, ECG, and Vital Signs Measurements

Procedure Study Day	Predose	Hours post dose										
		1	2	3	4	5	6	8	10	12	16	24
Blood sampling balovaptan, M2, and M3												
Period 1												
Day 1, 3, 5, 8, 9	X[a]											
Day 10	X[a]	X	X	X	X	X	X	X	X	X	X[b]	X[b]
Period 2												
Day 6, 8, 10, 13, 14, 16, 18, 19	X[a]											
Day 15	X[a]	X	X	X	X	X	X	X	X	X	X[c]	X[c]
Day 20	X[a]	X	X	X	X	X	X	X	X	X	X[d]	X[d]
Blood sampling itraconazole and hydroxyl-itraconazole												
Period 2												
Day 5	X[a]		X		X			X				
Day 6, 8, 10, 14, 15, 16, 18, 19	X[a]											
Day 20	X[a]		X		X			X				X[c]
12-lead electrocardiograms												
Period 1												
Days 1 and 10	X											
Period 2												
Day 1	X[e]											
Day 5, 6, 8, 10, 13, 15,17, 20	X				X							
Vital signs												
Period 1												
Day 1	X											
Day 11[f]												
Period 2												

Procedure Study Day	Predose	Hours post dose									
		1	2	3	4	5	6	8	10	12	16	24
Day 1	X[e]											
Day 6	X	X	X		X			X		X		
Day 8, 10, 13, and 17	X				X							
Day 15	X	X	X		X			X		X		
Day 21[f]												

[a]10 minutes predose (or time matched, when not dosed)
[b]Day 11
[c]Day 16
[d]Day 21
[e]Pre-AM dose
[f]Prior to 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 by Treatment, Analysis Day and Time-Point	PK
Table 14.2.2	Individual Values and Descriptive Statistics of Balovaptan Plasma Parameters by Treatment and Analysis Day	PK
Table 14.2.3	Individual Values and Descriptive Statistics of Balovaptan Metabolite (M2 and M3) Plasma Concentrations by Treatment, Analysis Day and Time-Point	PK
Table 14.2.4	Individual Values and Descriptive Statistics of Balovaptan Metabolite (M2 and M3) Plasma Parameters by Treatment and Analysis Day	PK
Table 14.2.5	Individual Values and Descriptive Statistics of Itraconazole and OH-Itraconazole Plasma Concentrations by Treatment, Analysis Day and Time-Point	PK
Table 14.2.7	Statistical Analysis of the effect of Itraconazole on Balovaptan	PK
Table 14.2.8	Statistical Analysis of the effect of Itraconazole on Balovaptan Metabolites (M2 and M3)	PK
Figure 14.2.10	Geometric Mean Balovaptan Plasma Concentrations versus Time by Treatment and Analysis Day (Linear and Semi-Logarithmic Scale)	PK
Figure 14.2.11	Geometric Mean Balovaptan Metabolite (M2 and M3) Plasma Concentrations versus Time by Treatment and Analysis Day (Linear and Semi-Logarithmic Scale)	PK
Figure 14.2.12	Geometric Mean Itraconazole and OH-Itraconazole Plasma Concentrations versus Time by Treatment and Analysis Day (Linear and Semi-Logarithmic Scale)	PK
Figure 14.2.13	Combined Individual Balovaptan Plasma Concentrations versus Time by Treatment and Analysis Day (Linear and Semi-Logarithmic Scale)	PK
Figure 14.2.14	Combined Individual Balovaptan Metabolite (M2, M3) Plasma Concentrations versus Time by Treatment and Analysis Day (Linear and Semi-Logarithmic Scale)	PK
Figure 14.2.15	Combined Individual Itraconazole and OH-Itraconazole Plasma	PK

	Concentrations versus Time by Treatment and Analysis Day (Linear and Semi-Logarithmic Scale)	
Figure 14.2.16	Individual Balovaptan Plasma Concentrations versus Time in Days by Treatment (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.17	Individual Balovaptan Metabolite (M2, M3) Plasma Concentrations versus Time in Days by Treatment (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.18	Individual Itraconazole and OH-Itraconazole Plasma Concentrations versus Time in Days (Linear and Semi-Logarithmic Scale)	Safety
Figure 14.2.19	Geometric Mean Trough Balovaptan Plasma Concentrations versus Time by Treatment (Linear and Semi-Logarithmic Scale)	PK
Figure 14.2.20	Geometric Mean Trough Balovaptan Metabolite (M2, M3) Plasma Concentrations versus Time by Treatment (Linear and Semi-Logarithmic Scale)	PK
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 14.3.3.1	Descriptive Statistics of Vital Signs	Safety
Table 14.3.3.1	Summary of 12-Lead Electrocardiogram	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
03-Aug-2018	[redacted]	Created from EDSREP 009 T 01 G template
28-Sep-2018		Sponsor comments included
09-Nov-2018		Additional sponsor addressed
14-Nov-2018		Statistical model for DDI analysis clarified after discussion with [redacted]