

**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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## PROTOCOL

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**MEDICAL MONITOR:** [REDACTED], MD

**SPONSOR:** F. Hoffmann-La Roche Ltd

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## FINAL PROTOCOL APPROVAL

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**Date and Time (UTC)**

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## PROTOCOL ACCEPTANCE FORM

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**MEDICAL MONITOR:** [REDACTED], MD

**SPONSOR:** F. Hoffmann-La Roche Ltd

**I agree to conduct the study in accordance with the current protocol.**

\_\_\_\_\_  
Principal Investigator's Name (print)

\_\_\_\_\_  
Principal Investigator's Signature

\_\_\_\_\_  
Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor to the contact provided below.

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## PROTOCOL SYNOPSIS

**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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**INDICATION:** Not applicable

**SPONSOR:** F. Hoffmann-La Roche Ltd

### **Objectives and Endpoints**

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

<b>Objectives</b>	<b>Endpoints</b>
<b>Primary</b>	
To investigate the effect of itraconazole treatment on the PK of balovaptan and its major metabolites M2 (as applicable) and M3, at steady state	Primary PK endpoints: balovaptan, M2, and M3 maximum observed plasma concentration ( $C_{max}$ ) and area under the concentration vs time curve over the dosing interval ( $AUC_{0-t}$ ) after 15 days of balovaptan once daily (qd) dosing in Period 2, and after 10 days of balovaptan qd dosing in Period 1  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
<b>Secondary</b>	
To explore the safety and tolerability of balovaptan when given alone and in combination with itraconazole in healthy subjects	Adverse events (AEs), clinical laboratory values, vital signs, electrocardiogram (ECG), and physical examination

<b>Tertiary/Exploratory</b>	
Relationship between the CYP3A4 genotype, among others <sup>a</sup> , and steady state balovaptan exposure, and the influence of the CYP3A4 genotype, among others, on the effect of itraconazole on balovaptan PK	The pharmacogenetics <sup>d</sup> of metabolizing enzymes, transferases, transporters, etc, possibly involved in the absorption, distribution, metabolism and excretion of balovaptan and its major metabolites (eg, CYP3A4 and P-glycoprotein)
The plasma exposure of itraconazole and hydroxy-itraconazole	Area under the concentration vs time curve from time 0 to 24 hours (AUC <sub>0-24h</sub> ), C <sub>max</sub> , and T <sub>max</sub> on Day 5 and Day 20

<sup>a</sup>The relationship between other genotypes and PK of balovaptan may also be explored

<sup>b</sup>Results may be pooled with data from other studies of balovaptan.

### **Study Design**

This study will be a 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 receive the following study drugs in 2 periods over a total of 37 days:

#### **Period 1:**

- Days 1 to 10: oral balovaptan qd
- Days 11 to 17: no study drug

#### **Period 2:**

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

For each study period, subjects will be admitted on Day -1, and dosing will begin on Day 1. 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.

The study will begin with 4 sentinel subjects in the initial cohort (Cohort A) in which the balovaptan dose will be 5 mg qd. Depending on the safety, tolerability and PK data of Cohort A, the remainder of subjects (Cohort B) may be dosed with balovaptan 5 mg qd or 10 mg qd. The dose may be increased to 10 mg qd for Cohort B if the highest exposure values for C<sub>max</sub> and AUC<sub>[0-τ]</sub> 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 in a previous study, and there are no prohibitive safety findings based on a review of safety data from Cohort A by the Sponsor's Medical Monitor or designee and the Investigator. If these criteria are not met, dosing will be continued at 5 mg qd in Cohort B.

If the Cohort B balovaptan dose remains at 5 mg qd, 10 subjects will be enrolled in Cohort B. If the dose is increased to 10 mg qd, 14 subjects will be enrolled.

### **Number of Subjects**

A total of 14 to 18 subjects will be enrolled. Enrolled subjects who withdraw from the study may be replaced at the discretion of the Investigator and Sponsor to ensure adequate numbers of evaluable subjects.

### **Target Population**

Healthy male (at least 50% of enrolled subjects) and female subjects between 18 to 65 years of age, inclusive.

### Inclusion Criteria

Subjects must meet the following criteria for study entry:

1. Healthy male and female subjects, aged 18 to 65 years, inclusive, at Screening. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, urinalysis, and serology.
2. Body Mass Index of 18 to 30 kg/m<sup>2</sup>, inclusive, at Screening.
3. For women of childbearing potential: agreement to use at least 2 acceptable contraceptive methods during the treatment period and for 90 days after the last dose of study drug.  

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ( $\geq 12$  continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

The following are acceptable contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide (male and female condom must not be used simultaneously); and cap, diaphragm, or sponge with spermicide.

Hormonal contraceptive methods must be supplemented by a barrier method.
4. For men: agreement to use contraceptive measures, and agreement to refrain from donating sperm, as defined below.  

With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for until 90 days after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
5. Able to participate and willing to give written informed consent and to comply with the study restrictions.
6. Fluent in English or Dutch.

### Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study entry:

1. Female subjects who are of childbearing potential who do not agree to use at least 2 acceptable methods of contraception. Female subjects who had tubal ligation who do not agree to use a barrier method of contraception.
2. Female subjects who are pregnant or lactating.
3. Any condition or disease detected during the medical interview/physical examination that would render the subject unsuitable for the study, place the subject at undue risk or interfere with the ability of the subject to complete the study in the opinion of the Investigator.
4. In the opinion of the Investigator, any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first study drug administration.
5. History of any clinically significant gastrointestinal, renal, hepatic, broncho-pulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological, lymphatic, musculoskeletal, genitourinary, immunological, dermatological or connective tissue or allergic disease, metabolic disorder, or cancer.
6. No signs and symptoms potentially indicative of peripheral neuropathy.
7. History or evidence of any medical condition potentially altering the absorption, metabolism or elimination of drugs. Surgical history of the gastrointestinal tract affecting gastric motility or altering the gastrointestinal tract, with the exception of uncomplicated appendectomy, which is allowed.
8. A history of clinically significant hypersensitivity (eg, to drugs, including itraconazole and balovaptan, and excipients) or allergic reactions.

9. Known personal or family history of congenital long QT syndrome or sudden death.
10. History or presence of clinically significant ECG abnormalities before study drug administration.
11. Subjects with screening or predose baseline mean QT interval corrected using Fridericia's formula (QTcF) >450 msec or <300 msec (using the same upper QTcF limit in both males and females).
12. Notable resting bradycardia (mean heart rate [HR] <40 bpm) on screening or predose baseline ECG. Notable resting tachycardia (mean HR > 90 bpm) on screening or predose baseline ECG.
13. Screening or baseline ECGs with QRS and/or T-wave judged to be unfavorable for a consistently accurate QT measurement (ie, neuromuscular artifact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T-wave, merged T- and U-waves, prominent U-waves, etc).
14. Screening or baseline ECG with evidence of clinically relevant abnormalities, e.g. atrial fibrillation, atrial flutter, complete bundle branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.
15. Confirmed (based on the average of  $\geq 3$  consecutive measurements) systolic blood pressure greater than 139 or less than 90 mmHg, and diastolic blood pressure greater than 89 or less than 45 mmHg.
16. Subjects experiencing fainting or pre-syncope events during orthostatic challenge testing at screening.
17. Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel, and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated on Day -1 of Period 1 to confirm eligibility.
18. History of coagulopathies, bleeding disorders, or blood dyscrasias.
19. Subjects who have smoked within 3 months prior to first dose administration.
20. Any clinically relevant history or any suspicion of alcohol and/or other substance abuse or addiction. Past alcohol and/or other substance abuse or addiction is also not allowed.
21. Alcohol consumption of >24 units per week for males and females. One unit of alcohol equals  $\frac{1}{2}$  pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or  $\frac{1}{6}$  gill (25 mL) of spirits.
22. Positive urine alcohol test or urine drug screen at screening or Day -1 of each treatment period (barbiturates, benzodiazepines, methadone, amphetamines [including ecstasy], methamphetamines, opiates, cocaine, and cannabinoids).
23. Positive result on human immunodeficiency virus (HIV) 1, HIV 2, hepatitis C virus antibody, or hepatitis B virus surface antigen.
24. Participation in an investigational drug or device study within 90 days prior to first dosing, or within 5 months prior to first dosing in case of a study with a biological, as calculated from the day of follow-up from the previous study.
25. Any donation of blood or plasma or significant blood loss within 3 months prior to screening.
26. Dietary restrictions that would prohibit the consumption of standardized meals.
27. Use of any prohibited medications and food before study start and subjects who do not agree to refrain from consuming prohibited medications or food during the study.
28. Subjects likely to need concomitant medication during the study (including for dental conditions).
29. Subjects who have received any prescribed systemic or topical medication within 14 days of the first dose administration, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety. Subjects who have received slow release medicinal formulations considered to still be active within 14 days of the first dose administration will also be excluded unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety.

30. Used the following within 7 days before the first study drug administration, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety:
  - Any non-prescribed systemic or topical medication
  - Herbal remedies.Paracetamol (up to 4 g/day within 7 days before study drug administration and 2 g/day within 48 hours before study drug administration), dietary supplements, vitamins and minerals, hormonal contraceptives and hormone replacement therapy are allowed.
31. Received any medications known to chronically alter drug absorption or elimination processes within 4 weeks before the first study drug administration, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety.
32. Use of any drugs or substances, including herbal treatments such as St John's Wort, that are known to be substrates, inducers or inhibitors of CYP3A4 within 4 weeks before the first study drug administration.
33. Subjects under judicial supervision, guardianship, or curatorship.
34. Poor venous access for blood sampling.
35. Subjects who have previously taken part in or withdrawn from this study.
36. Subjects who are unwilling to practice safe sex (use male or female condom) for the duration of the study.

#### **End of Study**

The end of this study is defined as the date when the last subject, last visit occurs or safety follow-up is received from the last subject, whichever occurs later. The end of the study is expected to occur 12 weeks after the last subject is enrolled.

#### **Length of Study**

The total length of the study, from screening of the first subject to the end of the study, is expected to be approximately 15 weeks.

#### **Investigational Medicinal Products**

Balovaptan (Test Product/Investigational Drug): 5 mg dispersible tablets and 10 mg film-coated tablets

Itraconazole: 100 mg capsule

#### **Statistical Methods**

##### **Primary Analysis**

The primary PK parameters are  $C_{max}$  and  $AUC_{0-T}$  for balovaptan, M2, and M3 on Day 10 of Period 1 and Day 20 of Period 2.

A linear mixed model analysis will be applied to analyze the log-transformed primary PK parameters. The model assumes fixed effect for treatment and a random effect for subject. Estimates of geometric mean ratios together with the corresponding 90% CIs will be derived for the comparisons of the PK parameters as follows:

- balovaptan plus itraconazole (test) vs balovaptan alone (reference)

##### **Determination of Sample Size**

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 for 10 days to ensure a minimum of 12 completers. The sample size was chosen based on balovaptan within-subject variability (CV%) of around 39% for  $AUC_{0-T}$  and 36% for  $C_{max}$  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.

#### **Interim Analyses**

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.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASD	Autism Spectrum Disorder
AST	aspartate aminotransferase
AUC <sub>0-τ</sub>	area under the concentration vs time curve over the dosing interval
AUC <sub>0-24h</sub>	area under the concentration vs time curve from time 0 to 24 hours
AUC <sub>0-120h</sub>	area under the concentration vs time curve from time 0 to 120 hours
C <sub>max</sub>	maximum observed plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
CRO	contract research organization
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
C <sub>trough</sub>	trough plasma concentration
CYP	cytochrome P450
DDI	drug-drug interaction
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EU	European Union
FSH	follicle-stimulating hormone
GLP	Good Laboratory Practice
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	Heart rate
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
MAD	multiple ascending dose



NOAEL	no observed adverse effect level
NOEL	no observed effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PND	postnatal day
qd	once daily
QTcF	QT interval corrected using of Fridericia's formula
SAD	single ascending dose
SAE	serious adverse event
T <sub>1/2</sub>	half-life
T <sub>max</sub>	time to maximum observed plasma concentration
ULN	upper limit of normal
V1a	vasopressin receptor 1A
WBC	white blood cell

## 1. **BACKGROUND**

### 1.1 **AUTISM SPECTRUM DISORDER**

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by two core domains: impairments in social interaction and communication and the presence of repetitive or restricted behaviors, interests, or activities (American Psychiatric Association, 2013). The Autism and Developmental Disabilities Monitoring Network recently reported, based on children records, that the estimated prevalence of ASD in the United States for the year 2010 was 14.7 per 1000 (one in 68) children aged 8 years (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, 2014). Core symptoms of ASD affecting domains of socialization, communication, and repetitive behavior are usually observed by 3 years of age, although typical language development might delay identification of symptoms.

Deficits in socialization manifest themselves as impaired use of non-verbal communication, delayed and reduced interactions with peers, absent sharing of enjoyable experiences and interest with peers, and lack of social judgment. Abnormalities in communication include a delay in verbal language development, impaired expressive language, deficient language pragmatics, as well as stereotyped, repetitive, or idiosyncratic use of language. Stereotyped and repetitive behavior manifests as a preoccupation with stereotyped or restricted interests, adherence to routines, rigidity, and perseverative and stereotyped behavior, motor mannerisms, and preoccupation or fascination with parts of items, and unusual visual exploration (Levy et al., 2009). In addition to these core deficits, patients with ASD suffer from a range of co-morbid conditions, including irritability, depression or anxiety, attention deficits, obsessive compulsive symptoms, seizures, and sleep disruption. Functional and structural deficits in the brain network disrupt the typical processing of social cues (such as faces and speech) leading to diminished social affiliative behavior which has been implicated in the core symptom of abnormal socialization associated with ASD. Abnormalities have been found in key areas including structures in the superior temporal lobe, fusiform gyrus, amygdala, and prefrontal cortex. At present, no pharmacological treatment exists for the core deficits of ASD. Currently available pharmacological treatments address only the symptoms associated with autism (irritability, sleep, anxiety, etc). Non-pharmacological treatments have been developed to address the core symptoms; however, efficacy has not been proven in large clinical trials (Meyer-Lindenberg et al., 2009). Accordingly, there is a big unmet medical need for pharmacological treatments that target and modify these key deficits.

The etiology of ASD is highly genetic, although environmental factors also contribute to the overall risk. Heritability estimates from family and twin studies suggest that about 90% of variance can be attributed to genetic factors, making ASD a neuropsychiatric disorder that is highly affected by genetic factors. The vasopressin system has been implicated in autism by studies of the arginine vasopressin receptor 1A gene, which encodes the vasopressin receptor 1A (V1a) and is located on chromosome 12q (Meyer-Lindenberg et

al., 2009). Both over- and under-transmission of specific but different alleles of this gene have been reported in autistic individuals and are associated with specific traits. One of these risk alleles has been found to increase activation of the amygdala during face processing and is associated with increased V1a receptor messenger RNA levels in the human hippocampus post-mortem. In particular, both nonclinical and clinical research supports a specific role of vasopressin in affiliative behavior.

In healthy subjects, intranasal vasopressin administration has been shown to increase the perception of ambiguous social stimuli as threatening and to impair emotion recognition in males. In non-human mammals, vasopressin receptors are distributed in various brain regions associated with central nervous system (CNS) control of stress and anxiety and, more importantly in this context, with social behavior, including parental care, pair-bonding, social memory, and social aggression. Specifically, vasopressin has been implicated more in male-typical social behaviors, including aggression, pair-bond formation, scent marking, and courtship. Recently, vasopressin was found to affect social recognition and interaction in rodents via its modulatory effect on olfaction (Tobin et al., 2010) – a sensory modality that may also be impaired in autism (May et al., 2011).

In summary, evidence from both human and animal studies strongly implicates the V1a receptor in mediating and modulating key social behaviors that are deficient in ASD. Together with the known negative effects of intranasal administration of vasopressin on emotional cognition, a V1a receptor antagonist may provide a novel and first approach to treat the deficits at the core of these disorders.

Balovaptan (RO5285119) is a potent and selective human V1a receptor antagonist that blocks the activation of the V1a G protein-coupled receptor.

## **1.2 BACKGROUND ON BALOVAPTAN**

Chronic administration of balovaptan reversed social behavior and cognitive impairments induced by prenatal valproate treatment in rats, an animal model that reflects some of the behavioral changes seen in patients with ASD. [REDACTED]

The in vitro metabolism of balovaptan was studied in hepatic preparations from human, rat, dog, minipig, cynomolgus monkey, mouse, and rabbit. [REDACTED]

The in vivo pharmacokinetic (PK) studies with balovaptan were conducted in rats, dogs, and cynomolgus monkeys. In animals, balovaptan showed a high (rats) to moderate or low (dogs and cynomolgus monkeys) plasma clearance and moderate extravascular

distribution. High to moderate bioavailability, depending on the species, was observed after oral application. In human, 2 major metabolites, M2 (RO7045402) and M3 (RO5273004), have been identified, which are present in rats and dogs. M2 and M3 are also V1a antagonists. Balovaptan and M2 are mainly metabolized through cytochrome P450 (CYP)3A4. Balovaptan and M3 have been shown in vitro to be strong, substrate-dependent P-glycoprotein (P-gp) inhibitors.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### **1.2.1 Previous and Ongoing Clinical Studies**

To date, balovaptan has been investigated in 5 completed Phase I studies including a proof-of-mechanism study in healthy volunteers (BP29412) in a total of 195 subjects. A Phase I relative bioavailability study (Study WP40038) comparing the Phase III tablet formulation with formulations used in previous Phase I and II studies is ongoing (clinically complete, reporting ongoing).

A Phase II study in 148 adult male ASD patients has been completed (BP28420, also referred to as VANILLA) and a Phase II study in 127 pediatric ASD patients (male and female) is ongoing (BP30153, also referred to as AV1ATION).

#### **1.2.1.1 Clinical Pharmacology**

Exposure of balovaptan increased in a greater than dose-proportional manner following single doses of 0.5 to 76 mg, whereas an approximately linear increase in exposure was observed after repeated dosing with 12 to 52 mg once daily (qd) for 14 days. Balovaptan was rapidly absorbed with a median time to maximum observed plasma concentration ( $T_{max}$ ) between 1 and 4.5 hours after administration of single doses and between 3 and 4 hours following multiple dosing. Steady state was achieved after approximately 7 days; the mean apparent elimination half-life ( $T_{1/2}$ ) after the last dose (Day 14) was approximately 46 hours. Food had no relevant effect on the PK of balovaptan.

In the human mass balance study (Study BP29279), an almost complete absorption of the study drug was observed within the first 72 hours following administration.

The majority of excretion of drug-related material occurred within the first 7 days. Renal excretion was found to be the major pathway of elimination (approximately 53% of the material recovered, mostly composed of metabolites) with the primary route of excretion via metabolism to M1 ( [REDACTED] ) into urine, accounting for approximately 23% of the dose. A further 30% of the administered dose was recovered in feces.

In plasma, steady state exposure to the [REDACTED] metabolite M3 was similar to or slightly higher than that of balovaptan and exposure to the [REDACTED] metabolite M2 was lower than that of parent. M3 and M2 qualify as major metabolites in plasma.

[REDACTED]

There was no clinically/statistically relevant PK interaction with the P-glycoprotein substrate risperidone, one of only 2 approved medications for ASD symptoms in the US, and fluoxetine, a weak CYP3A4 inhibitor often used to treat associated symptoms of ASD. Administration of a single dose of balovaptan 12 mg in combination with itraconazole, a strong CYP3A4 inhibitor, resulted in an increase in the exposure of balovaptan by 1.4-fold for  $C_{max}$  and an approximately 3.1-fold increase for area under the concentration vs time curve from time 0 to 120 hours ( $AUC_{0-120h}$ ). The exposure of metabolite M3 was 1.92- and 1.82-fold lower in terms of  $C_{max}$  and  $AUC_{0-120h}$ , respectively.

#### **1.2.1.2 Safety**

To date, balovaptan has been found to be safe and well tolerated in clinical trials. No particular safety concern has emerged and no adverse drug reactions have been identified. More specifically, creatine phosphokinase (CPK) was monitored in previous trials based on observations of muscle toxicity in rats; no changes of any importance were noticed. Similarly, no hematology or neurotoxicity findings have been observed in clinical trials. The maximum tolerated dose was not reached in either the single ascending dose (SAD) study with single doses (up to 76 mg) or the multiple ascending dose (MAD) study with multiple doses (up to 52 mg qd for 14 days) in healthy subjects. In light of convulsions observed in dogs, dose escalation was stopped so as not to exceed a  $C_{max}$  (mean) of 810 ng/mL in the SAD and MAD studies. In healthy volunteer studies, one serious adverse event (SAE) of bacterial infection (suspected Lyme disease) was reported in Study BP29412; this SAE was considered unrelated to study drug.

Balovaptan has also been found to be safe and well tolerated in male patients with ASD at doses up to 10 mg/day (highest dose administered) for a period of 12 weeks (Study BP28420). No particular safety patterns attributable to the administration of balovaptan were identified. A total of 8 SAEs (all but one [rhabdomyolysis] considered unrelated to study drug) in 4 patients and 1 adverse event of special interest

(neutropenia) were reported in the study. No relevant safety concern has emerged from the recently started study in ASD pediatric patients (BP30153).

Based on the review of all available data, it is currently recommended not to exceed a plasma exposure equivalent to 20 mg qd in adult subjects in clinical trials with a continuous treatment duration longer than 4 weeks.

Refer to the Investigator's Brochure for details on nonclinical and clinical studies.

### **1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT**

The study will be performed in healthy subjects who will not receive any health benefit from participating in this study. The study is necessary for the further development of balovaptan and may be of benefit for future patients.

To date, balovaptan has been investigated in 195 healthy subjects in 5 completed Phase 1 studies (Studies BP25694, BP28318, BP28977, BP29279, and BP29412). One oral relative bioavailability study (Study WP40038) is ongoing (clinically complete, reporting ongoing).

Additionally, balovaptan was investigated in a Phase II study in 148 adult male patients with ASD (BP28420, "VANILLA").

Adverse event (AE) reporting in healthy subjects did not reveal any particular safety alert for balovaptan. The most frequently reported AE was headache, without an apparent dose-response relationship for balovaptan. For the vast majority of AEs, the intensity was rated as mild or moderate. The dose range in these studies was 0.5 to 76 mg (single dose) and 12 to 52 mg (multiple doses for 14 days).

The effect of inhibition of CYP3A4 was previously investigated using a single dose of 12 mg of balovaptan. The study showed that balovaptan  $AUC_{0-120h}$  increased by 3.1-fold and  $C_{max}$  by 1.4-fold in the presence of itraconazole. Mean  $AUC_{0-120h}$  and  $C_{max}$  metabolite M3 were 1.82- and 1.92-fold lower, respectively, in the presence of itraconazole than in the absence of itraconazole. M2 was not measured in that study.

The current study is designed to assess the effect of inhibition of CYP3A4 on the steady state pharmacokinetics of balovaptan after 15 days of coadministration with itraconazole, as balovaptan showed dose and time-dependent PK. Although not reliably measured, analysis of  $AUC_{0-inf}$  in the presence of itraconazole indicated a 4.6-fold increase in balovaptan exposure and plasma  $T_{1/2}$  indicated an increase from 27 to 80 hours. The mean (SD)  $C_{max}$  and  $AUC_{0-T}$  for parent following 14 days of dosing with balovaptan 52 mg qd was 484 (43.1) ng/mL and 5920 (817) h·ng/mL, respectively. M3 was only measured after balovaptan 40 mg for 14 days: the mean (SD)  $C_{max}$  and  $AUC_{0-T}$  were 264 (45.4) ng/mL and 5260 (807) and h·ng/mL, respectively.

Due to the anticipated increase in balovaptan exposure when administered with itraconazole, to ensure optimal subject safety, the study design includes a sentinel group of 4 subjects, who will be dosed with 5 mg balovaptan qd. The dose may be increased to the targeted clinical dose, 10 mg, only if exposure data from the sentinel cohort are acceptable (see Section 3.1 for exposure criteria), and no safety concerns have emerged in the opinion of the Investigator or Sponsor's Medical Monitor.

Itraconazole is generally well tolerated. Gastrointestinal disturbances are the most frequently reported AEs following the oral use of itraconazole. Nausea and vomiting have been reported in about 11% and 5% of patients undergoing treatment of systemic fungal infections, respectively, diarrhea in 3%, and abdominal pain in about 2%. These AEs are dose-related and may be minimized by giving itraconazole with food. Rash was observed in 9% of patients, however rash tends to occur more frequently in immunocompromised patients receiving immunosuppressive medications. Itraconazole has been associated with rare cases of serious hepatotoxicity. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition, and some of these cases developed within the first week of treatment. Other adverse effects include pruritus and angioedema, and rare cases of anaphylaxis have been reported. Fatigue, headache, dizziness, hypertension, decreased libido, impotence, and somnolence may also occur (Janssen Pharmaceuticals, 2001).

## **2. OBJECTIVES AND ENDPOINTS**

This study will investigate the effect of itraconazole treatment on the PK of balovaptan and its major metabolites M2 and M3. [Table 1](#) presents the objectives and endpoints.



**Table 1 Objectives and Corresponding Endpoints**

<b>Objectives</b>	<b>Endpoints</b>
<b>Primary</b>	
To investigate the effect of itraconazole treatment on the PK of balovaptan and its major metabolites M2 (as applicable) and M3, at steady state	<p>Primary PK endpoints: balovaptan, M2, and M3 <math>C_{max}</math> and area under the concentration vs time curve over the dosing interval (<math>AUC_{0-T}</math>) after 15 days of balovaptan qd dosing in Period 2, and after 10 days of balovaptan qd dosing in Period 1</p> <p>Additional PK endpoints: balovaptan, M2, and M3 time to maximum observed plasma concentration (<math>T_{max}</math>), trough plasma concentration (<math>C_{trough}</math>), and time to steady state</p>
<b>Secondary</b>	
To explore the safety and tolerability of balovaptan when given alone and in combination with itraconazole in healthy subjects.	Adverse events (AEs), clinical laboratory values, vital signs, electrocardiogram (ECG), and physical examination
<b>Tertiary/Exploratory</b>	
Relationship between the CYP3A4 genotype, among others, <sup>a</sup> and steady state balovaptan exposure, and the influence of the CYP3A4 genotype, among others, on the effect of itraconazole on balovaptan PK	The pharmacogenetics <sup>b</sup> 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)
The plasma exposure of itraconazole and hydroxy-itraconazole	Area under the curve from time 0 to 24 hours ( $AUC_{0-24h}$ ), $C_{max}$ , and $T_{max}$ on Day 5 and Day 20

<sup>a</sup>The relationship between other genotypes and PK of balovaptan may also be explored<sup>b</sup>Results may be pooled with data from other studies of balovaptan.

### **3. STUDY DESIGN**

#### **3.1 DESCRIPTION OF THE STUDY**

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:

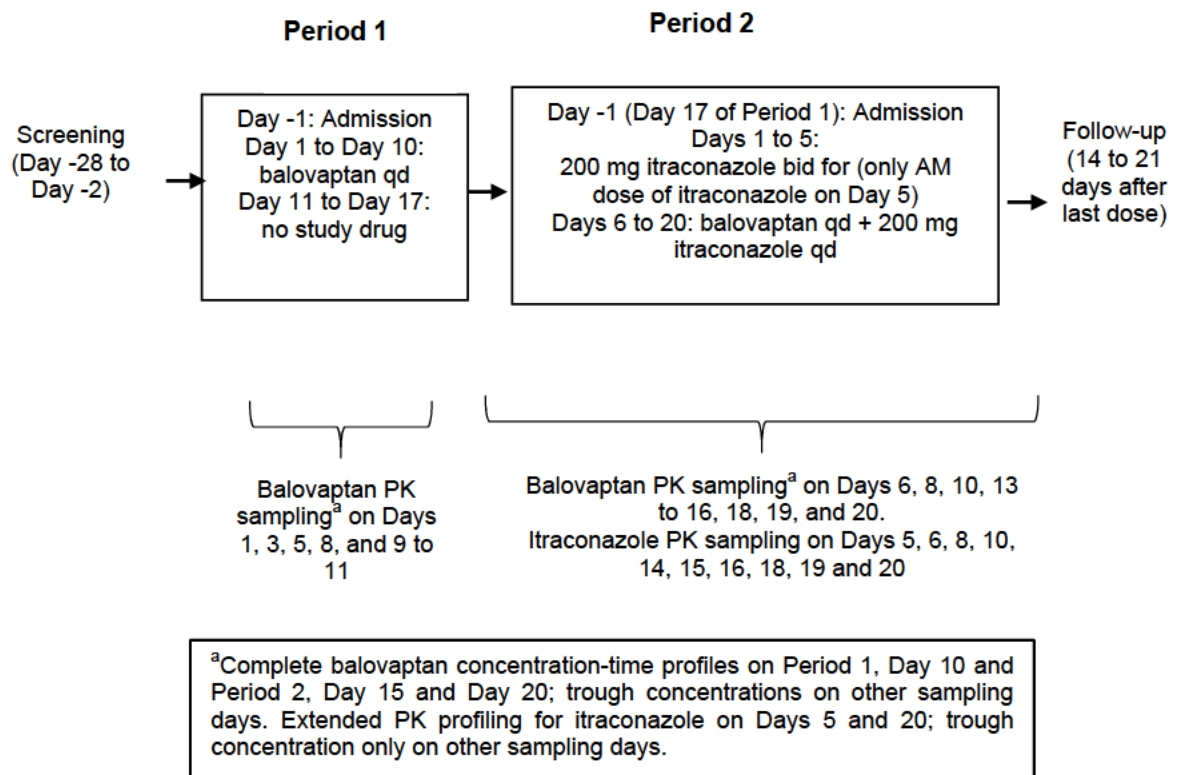
- Days 1 to 10: oral balovaptan once daily (qd)
- Days 11 to 17: no study drug

##### 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 1.

**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 1.

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  $AUC_{[0-1]}$  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 ( $484 \pm 43.1$  ng/mL for  $C_{max}$  and  $5920 \pm 817$  h-ng/mL for  $AUC_{tau}$ ) 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.

### **3.2 END OF STUDY AND LENGTH OF STUDY**

The end of this study is defined as the date when the last subject, last visit (LSLV) occurs or safety follow-up is received from the last subject, whichever occurs later. The end of the study is expected to occur 12 weeks after the last subject is enrolled.

The total length of the study, from screening of the first subject to the end of the study, is expected to be approximately 15 weeks.

### **3.3 RATIONALE FOR STUDY DESIGN**

#### **3.3.1 Rationale for Open Label Design**

The primary objective in this study is to assess to what extent exposure to balovaptan after repeat dosing may change in the presence of the CYP3A4 inhibitor itraconazole. As such, drug concentrations in plasma are assumed to be objective measurements, which cannot be affected by volunteer or staff behavior. This is different for tolerability reporting, for which it is conceivable that knowing what treatment is being administered may affect reporting or causality interpretation. Therefore, it is generally accepted to conduct drug-drug interaction (DDI) studies with PK or pharmacodynamic (PD) primary endpoints using an open-label design, without placebo treatments, and since evaluation of safety and tolerability is only a secondary objective, an open-label design was deemed appropriate.

#### **3.3.2 Rationale for Balovaptan and Itraconazole Dose and Schedule**

##### **3.3.2.1 Balovaptan**

A dose of 10 mg balovaptan has shown statistically significant changes in efficacy parameters in adult patients with ASD and is the current proposed dose for Phase 3 trials in adults. However, it is to be expected that exposure in the presence of itraconazole may increase, based on the effect of itraconazole on the exposure of a

single dose of 12 mg balovaptan (at least 3.1-fold increase in  $AUC_{0-120h}$  and 1.4-fold increase in  $C_{max}$ ).

Therefore, in the current study, the effect of itraconazole on the multiple dose PK of a low dose of 5 mg balovaptan qd will initially be assessed in a sentinel group of 4 subjects, in order to assess whether it will be safe to assess the effect of itraconazole on the higher, clinically relevant dose of 10 mg. Single doses of balovaptan up to 76 mg and multiple doses up to 52 mg qd for 14 days were well tolerated. The mean exposure seen with multiple dosing of balovaptan 52 mg was  $484 \pm 43.1$  ng/mL for  $C_{max}$  and  $5920 \pm 817$  h·ng/mL for  $AUC_{0-T}$ .

Balovaptan is being developed for use in ASD, so it is expected that patients will need to take it for prolonged periods of time, likely for years or for life. Hence multiple dose testing is relevant from a clinical point of view. The multiple dose PK of balovaptan with 14 days of dosing was previously characterized in humans and was found to be time and dose dependent. Accumulation was observed with multiple dosing, and steady state of parent and M3 was observed after approximately 7 days of dosing; the time to steady state has only been evaluated with sparse PK measurements for M2. Population modelling indicates that steady state of parent, M2, and M3 following a dose of balovaptan 10 mg is reached later (after around 10 days). In the presence of itraconazole, an increase in plasma  $T_{1/2}$  from 27 to 80 hours was observed. Based on these observations, the maximum level of DDI due to inhibition of CYP3A4 is expected to be observed with 15 days of coadministration of itraconazole with balovaptan, based on a predicted  $T_{1/2}$  of ~ 80 hours for balovaptan when combined with itraconazole.

In addition, exposure to the metabolite M2 has not been previously characterized with intensive PK sampling after multiple doses in humans, and this will also be achieved in the current design.

### **3.3.2.2 Itraconazole**

The proposed dose level and dosing regimen for itraconazole, to be used as an inhibitor of CYP3A4, is based on published recommendations (Liu et al, 2016). Itraconazole run-in will include 4 days of bid dosing of 200 mg plus 1 day of qd dosing in order to ensure that steady state inhibition has been achieved prior to administering the first dose of balovaptan on Day 6 of Period 2.

Itraconazole will be administered in the fed state as capsules, in order to maximize exposure to both parent itraconazole and hydroxy-itraconazole.

### **3.3.3 Rationale for Sentinel Group**

As an increase in balovaptan exposure when administered together with itraconazole is expected, to ensure optimal safety of subjects an initial sentinel cohort of 4 subjects (Cohort A) will be enrolled in which the dose of balovaptan will be 5 mg qd. The safety and 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 Sponsor's Medical Monitor or designee and the Investigator. After review of the data, a dose of balovaptan will be selected for the remainder of subjects (Cohort B). The balovaptan dose for Cohort B may remain at 5 mg qd or be increased to 10 mg qd. The dose may be increased to 10 mg qd for Cohort B if the highest exposure values for  $C_{max}$  and  $AUC_{[0-\tau]}$  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 (see Section 3.1) and there are no prohibitive safety findings based on a review of safety data from Cohort A by the Sponsor's Medical Monitor or designee and the Investigator.

### **3.3.4 Rationale for Study Population**

Healthy subjects have been chosen as the study population due to the low risk of clinically significant toxicity at anticipated exposure levels. Moreover, use of healthy subjects as opposed to patients will allow a clearer interpretation of the study results, as there will be no confounding factors that result from changes in disease state and/or concomitant medication use.

Female and male subjects may be included. Female subjects of childbearing potential must use 2 acceptable methods of contraception. Female subjects who have undergone tubal ligation must use a barrier method of contraception. Male subjects must agree to use contraceptive measures and agree to refrain from donating sperm. The study will enroll at least 50% male subjects, as ASD is more prevalent in males.

## **4. MATERIALS AND METHODS**

### **4.1 SUBJECTS**

The target population will be healthy male (at least 50% of enrolled subjects) and female subjects between 18 to 65 years of age, inclusive, on the day of screening. Between 14 and 18 subjects will be enrolled. Enrolled subjects who withdraw from the study may be replaced at the discretion of the Investigator and Sponsor to ensure adequate numbers of evaluable subjects.

#### **4.1.1 Inclusion Criteria**

Subjects must meet the following criteria for study entry:

1. Healthy male and female subjects, aged 18 to 65 years, inclusive, at Screening. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, urinalysis, and serology.
2. Body Mass Index (BMI) of 18 to 30 kg/m<sup>2</sup>, inclusive, at Screening.

3. For women of childbearing potential: agreement to use at least 2 acceptable contraceptive methods during the treatment period and for 90 days after the last dose of study drug.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ( $\geq 12$  continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

The following are acceptable contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide (male and female condom must not be used simultaneously); and cap, diaphragm, or sponge with spermicide.

Hormonal contraceptive methods must be supplemented by a barrier method.

4. For men: agreement to use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 90 days after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

5. Able to participate and willing to give written informed consent and to comply with the study restrictions.
6. Fluent in English or Dutch.

#### **4.1.2 Exclusion Criteria**

Subjects who meet any of the following criteria will be excluded from study entry:

1. Female subjects who are of childbearing potential who do not agree to use 2 acceptable methods of contraception. Female subjects who had tubal ligation who do not agree to use a barrier method of contraception.
2. Female subjects who are pregnant or lactating.
3. Any condition or disease detected during the medical interview/physical examination that would render the subject unsuitable for the study, place the subject at undue risk or interfere with the ability of the subject to complete the study in the opinion of the Investigator.
4. In the opinion of the Investigator, any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first study drug administration.
5. History of any clinically significant gastrointestinal, renal, hepatic, broncho-pulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological, lymphatic, musculoskeletal, genitourinary, immunological, dermatological or connective tissue or allergic disease, metabolic disorder, or cancer.

6. Signs and symptoms potentially indicative of peripheral neuropathy
7. History or evidence of any medical condition potentially altering the absorption, metabolism, or elimination of drugs. Surgical history of the gastrointestinal tract affecting gastric motility or altering the gastrointestinal tract, with the exception of uncomplicated appendectomy, which is allowed.
8. A history of clinically significant hypersensitivity (eg, to drugs, including itraconazole and balovaptan, and excipients) or allergic reactions.
9. Known personal or family history of congenital long QT syndrome or sudden death.
10. History or presence of clinically significant ECG abnormalities before study drug administration.
11. Subjects with screening or predose baseline mean QT interval corrected using Fridericia's formula (QTcF) >450 msec or <300 msec (using the same upper QTcF limit in both males and females).
12. Notable resting bradycardia (mean HR <40 bpm) on screening or predose baseline ECG. Notable resting tachycardia (mean HR > 90 bpm) on screening or predose baseline ECG.
13. Screening or baseline ECGs with QRS and/or T-wave judged to be unfavorable for a consistently accurate QT measurement (ie, neuromuscular artifact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T-wave, merged T- and U-waves, prominent U-waves, etc.).
14. Screening or baseline ECG with evidence of clinically relevant abnormalities, e.g. atrial fibrillation, atrial flutter, complete bundle branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.
15. Confirmed (based on the average of  $\geq 3$  consecutive measurements) systolic blood pressure greater than 139 or less than 90 mmHg, and diastolic blood pressure greater than 89 or less than 45 mmHg.
16. Subjects experiencing fainting or pre-syncopal events during orthostatic challenge testing at screening.
17. Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel, and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated on Day -1 to confirm eligibility.
18. History of coagulopathies, bleeding disorders, or blood dyscrasias.
19. Subjects who have smoked within 3 months prior to first dose administration.
20. Any clinically relevant history or any suspicion of alcohol and/or other substance abuse or addiction. Past alcohol and/or other substance abuse or addiction is also not allowed.
21. Alcohol consumption of >24 units per week for males and females. One unit of alcohol equals  $\frac{1}{2}$  pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or  $\frac{1}{6}$  gill (25 mL) of spirits.



22. Positive urine alcohol test or urine drug screen at screening or Day -1 of each treatment period (barbiturates, benzodiazepines, methadone, amphetamines [including ecstasy], methamphetamines, opiates, cocaine, and cannabinoids).
23. Positive result on human immunodeficiency virus (HIV) 1, HIV2, hepatitis C virus (HCV) antibody, or hepatitis B virus surface antigen (HBsAg).
24. Participation in an investigational drug or device study within 90 days prior to first dosing, or within 5 months prior to first dosing in case of a study with a biological, as calculated from the day of follow-up from the previous study.
25. Any donation of blood or plasma or significant blood loss within 3 months prior to screening.
26. Dietary restrictions that would prohibit the consumption of standardized meals.
27. Use of any prohibited medications and food before study start and subjects who do not agree to refrain from consuming prohibited medications or food during the study (see Section 4.4).
28. Subjects likely to need concomitant medication during the study (including for dental conditions).
29. Subjects who have received any prescribed systemic or topical medication within 14 days of the first dose administration, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety, and subjects who have received slow release medicinal formulations considered to still be active within 14 days of the first dose administration will also be excluded unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety.
30. Used the following within 7 days before the first study drug administration, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety:
  - any non-prescribed systemic or topical medication
  - herbal remedies.

Paracetamol (up to 4 g/day within 7 days before study drug administration and 2 g/day within 48 hours before study drug administration), dietary supplements, vitamins and minerals, hormonal contraceptives and hormone replacement therapy are allowed.

31. Received any medications known to chronically alter drug absorption or elimination processes within 4 weeks before the first study drug administration, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety.
32. Use of any drugs or substances, including herbal treatments such as St John's Wort, that are known to be substrates, inducers, or inhibitors of CYP3A4 within 4 weeks before the first study drug administration.
33. Subjects under judicial supervision, guardianship or curatorship.
34. Poor venous access for blood sampling.

35. Subjects who have previously taken part in or withdrawn from this study.
36. Subjects who are unwilling to practice safe sex (use male or female condom) for the duration of the study.

## **4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING**

This study will be non-randomized, open-label, one-sequence, two-period within-subject study.

Subjects who have met all eligibility criteria will receive a subject number upon inclusion in the study (subject numbers: 01 to 14 or 01 to 18). Subject numbers will be allocated sequentially in the order in which the subjects are enrolled. The subject number will ensure identification throughout the study. Replacement subjects (if needed) will receive the number of the subject to be replaced, increased by 100 (eg, 101 replacement number for subject number 01), and will be administered the same treatments in the same order.

Subjects who drop out or withdraw for any reason without completing all screening evaluations successfully, will be considered “screening failures”. Such subjects will not receive a subject number. The Investigator will keep a screening log of all subjects screened in order to assess the numbers and characteristics of the excluded subjects, and the reasons for their exclusion.

## **4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN**

The investigational medicinal products (IMPs) for this study are balovaptan and itraconazole.

### **4.3.1 Study Treatment Formulation, Packaging, and Handling**

#### **4.3.1.1 Balovaptan**

Balovaptan 5 mg will be supplied by the Sponsor as dispersible tablets in high-density polyethylene bottles. Balovaptan 10 mg will be supplied by the Sponsor as film-coated tablets in high-density polyethylene bottles. For information on the formulation and handling of balovaptan, see Investigational Medicinal Product Dossier.

#### **4.3.1.2 Itraconazole**

Itraconazole 100 mg capsules will be obtained commercially by the investigational site. For information on the formulation, packaging, and handling of itraconazole, see the local prescribing information for itraconazole.

### **4.3.2 Study Treatment Dosage, Administration, and Compliance**

The treatment regimens are summarized in Section [3.1](#).

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events

associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event Report Form.

Guidelines for treatment discontinuation for subjects who experience AEs are provided in Section 5.1.

#### **4.3.2.1 Balovaptan**

Balovaptan will be administered alone with food in the morning of Days 1 to 10 of Period 1, and in combination with itraconazole on Days 6 to 20 of Period 2. In both periods, study drugs will be swallowed whole with 240 mL of still water.

#### **4.3.2.2 Itraconazole**

Itraconazole will be administered with food in the morning and evening of Days 1 to 4 and in the morning of Days 5 to Day 20 of Period 2. On Days 6 to 20 of Period 2, itraconazole will be administered in combination with balovaptan. In both periods, the study drugs will be swallowed whole with 240 mL of still water.

#### **4.3.3 Investigational Medicinal Product Accountability**

Balovaptan will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced. Itraconazole will be obtained commercially by the site.

The IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Dispensing Form.

#### **4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS**

Concomitant therapy consists of any medication (eg, prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to protocol-mandated treatment from 14 days prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

##### **4.4.1 Permitted Therapy**

Subjects who use oral contraceptives or hormone replacement therapy should continue their use unchanged.

Acetaminophen/paracetamol is allowed up to a maximum dose of 2 g/day up to 48 hours prior to dosing and after the in-house period, but should not exceed 4 g total during the week prior to dosing.

##### **4.4.2 Prohibited Therapy**

Any prescribed systemic or topical medication within 14 days of the first dose administration will be prohibited until the follow-up visit, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety. Slow release medicinal formulations considered to still be active within 14 days of the first dose administration will also be prohibited until the follow-up visit, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety. This is with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator, the medical and safety monitor and the Roche clinical pharmacologist. All medication administered to manage AEs should be recorded on the Adverse Event Report Form

The following concomitant medications in particular are prohibited, unless an exception has been agreed as mentioned above.

- Any inhibitor of CYP3A taken within 4 weeks (or within 5 half-lives, whichever is longest) prior to study drug administration, including but not limited to the following drugs: ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, and cimetidine, until follow-up.
- Any inducer of CYP3A taken within 4 weeks prior to study drug administration, including but not limited to the following drugs: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, and St. John's wort, until follow-up.
- Investigational drug or device therapy (other than protocol-mandated study treatment) is prohibited 90 days prior to first dosing, or within 5 months prior to first dosing in case of a study with a biological, as calculated from the day of follow-up from the previous study of study treatment and during study treatment.

#### **4.4.3 Prohibited Food**

- Consumption of methylxanthine-containing products (eg, coffee, tea, cola, chocolate) will be forbidden 48 hours before balovaptan dosing and during the stay in the CRU.
- It is not permitted to take any nutrients known to modulate CYP3A activity (eg, grapefruit juice; Seville orange) during the in-house stay.

#### **4.4.4 Additional Restrictions**

- Between the Screening visit and follow-up, alcohol must be restricted to no more than 2 units per day (1 unit is 285 mL of beer, 125 mL of wine or 25 mL of spirits). Alcohol consumption will not be allowed 48 hours before balovaptan dosing and whilst staying in the study center. Random alcohol/drugs of abuse testing may be employed throughout the study period to verify compliance.
- Standardized meals similar in content will be served to all subjects at days and the times noted in [Appendix 1](#). On these days a standardized breakfast, lunch, snack, and dinner will be served at similar times of the day (the same meal for each respective meal time), and subjects will be required to complete the meal. All other meals will conform to the site's standards. Breakfast will be provided 30 minutes before dosing and completed within approximately 15 minutes prior to balovaptan or itraconazole dosing. While in the CRU, subjects will be allowed to consume water *ad libitum*, except for 1 hour before and 2 hours after oral dosing, and a maximum of 3 liters a day.
- Subjects will not be allowed to perform strenuous exercise within 96 hours before screening, Day -1 of Periods 1 and 2, and follow-up. Light ambulatory activities will be permitted, with the level of activities kept as similar as possible on all days in the CRU.

### **4.5 STUDY ASSESSMENTS**

The schedule of activities to be performed during the study is provided in [Appendix 1](#). All activities must be performed and documented for each subject.

Subjects will be closely monitored for safety and tolerability throughout the study.

#### **4.5.1 Informed Consent Forms and Screening Log**

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled subjects and for subjects who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that subjects meet all eligibility criteria before enrollment. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

#### **4.5.2 Medical History, Concomitant Medication, and Demographic Data**

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be performed at the time points specified in [Appendix 1](#). In addition, all medications (eg, prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the subject within 14 days prior to initiation of study treatment will be recorded. At follow-up, any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

#### **4.5.3 Physical Examinations**

A complete physical examination, performed at the time points specified in [Appendix 1](#), should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, neurologic systems; complaint-driven genitourinary examination may be performed. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event Report eCRF (and Adverse Event Report Form as appropriate).

#### **4.5.4 Vital Signs**

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and tympanic temperature at the timepoints indicated in [Appendix 1](#). Blood pressure and pulse rate measurements will be performed after the subject has rested in a supine position for at least 5 minutes.

##### **4.5.4.1 Orthostatic Challenge Testing**

During a 15-minute period during which subjects will remain in a supine position, blood pressure according to the Riva-Rocci method and pulse rate will be measured after 10 and 15 minutes. If the blood pressure deviates from the previous measurement by more than 5 mmHg, another 5-minute extension period will be added, and blood pressure and pulse rate will be obtained after 20 minutes in the supine position.

The subject will then be asked to erect rapidly into a standing position, and blood pressure and pulse rate will be assessed again 3 minutes after standing.

Standing blood pressure and pulse rates will be compared against the latest blood pressure and pulse rate values obtained in the supine position. Orthostatic hypotension

is defined as a decrease in systolic blood pressure by at least 20 mmHg and/or a decrease in diastolic blood pressure by at least 10 mmHg.

#### **4.5.5 Laboratory, Pharmacokinetic, and Genotyping Samples**

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final Clinical Study Report has been issued, except where specified otherwise.

When a subject withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the subject specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section [8.4](#).

##### **4.5.5.1 Laboratory Samples**

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: leukocytes, erythrocytes, hemoglobin, hematocrit, platelets, absolute differential count (neutrophil, eosinophils, basophils, monocytes, lymphocytes)
- Blood chemistry panel: sodium, potassium, chloride, bicarbonate, glucose (fasting), urea, creatinine, total and conjugated bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl-transferase, CPK
- Coagulation: prothrombin time (international normalized ratio) and activated thromboplastin time at screening only and at end of study visit
- Drugs of abuse, including cannabinoids, amphetamines (including ecstasy), methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates, will be measured in urine at Screening and on Day -1 of each study period.
- Urine alcohol test at Screening and on Day -1 of each study period.
- Viral serology at Screening: HIV-1 and HIV-2, HBsAg, HCV antibody.
- Pregnancy test

Follicle-stimulating hormone (FSH) test and beta-human chorionic gonadotropin (serum pregnancy test) will be performed at Screening in all females. At subsequent visits as noted in [Appendix 1](#), a serum pregnancy test will be performed in all females.

- Urinalysis: A midstream, clean-catch urine specimen will be collected for dipstick analysis of pH, glucose, leucocytes, nitrites, protein, and blood. Microscopy will be performed if abnormalities are observed and if it is deemed necessary by the Investigator or designee, in particular when blood or protein is positive or strong positive. If there is an explanation for the positive dipstick result, it should be recorded, and there is no need to perform laboratory for microscopy and culture.

#### **4.5.5.2 Pharmacokinetic Samples**

Plasma samples for PK analysis will be shipped to designated bioanalytical laboratories for analysis.

Plasma samples collected for PK analysis will be destroyed after the final Clinical Study Report has been issued.

#### **4.5.5.3 Genotyping Samples**

A mandatory 3 mL whole blood sample will be taken for DNA extraction from every subject during the study on Day -1 of Period 1. The DNA may be used to determine whether genes relating to drug-metabolizing enzymes and/or drug transporter enzymes affect the PK and/or the safety profile of balovaptan. Genotyping samples will be sent to the Sponsor or a designee for analysis. This specimen will be destroyed no later than 2 years after the final Clinical Study Report has been issued.

The Sponsor maintains confidentiality standards by coding each subject enrolled in the study through assignment of a unique subject identification number. This number is used to code the samples. Subject names are not included in samples that are sent for analysis.

#### **4.5.6 Electrocardiograms**

Triplicate 12-lead ECG will be performed at the times indicated in [Appendix 1](#).

#### **4.5.7 Columbia Suicide Severity Rating Scale**

The 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).

The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality.

The C-SSRS assessments will be completed by the Investigator or Research Physician at the time points as specified in [Appendix 1](#).

#### **4.5.8 Drug and Metabolite Concentration Measurements**

Plasma concentrations of balovaptan and its metabolites M3 and M2 will be measured using a specific and validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Plasma concentrations of itraconazole and its metabolite



hydroxy-itraconazole will also be measured using a separate, specific and validated LC-MS/MS method.

#### **4.5.9 Timing of Study Assessments**

If performed at the same timepoint, assessments should be prioritized as follows, while ensuring PK blood sampling is conducted at the scheduled time:

- 12-lead ECGs
- Vital signs measurements
- PK blood sampling
- Laboratory safety tests

#### **4.6 TREATMENT, SUBJECT, STUDY, AND SITE DISCONTINUATION**

##### **4.6.1 Study Treatment Discontinuation**

Subjects must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues to receive study treatment (see Section 5.1.2 for additional guidance on the management of toxicities and of subjects who experience AEs)
- Investigator or Sponsor determines it is in the best interest of the subject
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Subjects who discontinue study treatment prematurely may be replaced.

Subjects will return to the clinic for a follow-up visit 14 to 21 days after the last dose of study drug (see [Appendix 1](#) for additional details).

##### **4.6.2 Subject Discontinuation from Study**

Subjects will return to the clinic for a follow-up visit 14 to 21 days after the last dose of study drug.

Subjects have the right to voluntarily withdraw from the study at any time for any reason. In addition, the Investigator has the right to withdraw a subject from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Subject withdrawal of consent
- Study termination or site closure
- Subject non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator or Sponsor

Every effort should be made to obtain information on subjects who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a subject requests to be withdrawn from the study, this request must be documented in the source documents and signed by the Investigator. Subjects who withdraw from the study may be replaced.

#### **4.6.3 Study Discontinuation**

Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory

The Sponsor will notify the Investigator if the Sponsor decides to discontinue the study.

#### **4.6.4 Site Discontinuation**

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (ie, all subjects have completed the study and all obligations have been fulfilled)

### **5. ASSESSMENT OF SAFETY**

#### **5.1 SAFETY PLAN**

Balovaptan is not approved, and clinical development is ongoing. The safety plan for subjects in this study is based on clinical experience with balovaptan in completed and ongoing studies. Potential important safety risks for balovaptan are outlined below. Please refer to the RO5285119 (Balovaptan) Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of subjects participating in this study. Eligibility criteria have been designed to exclude subjects at higher risk for toxicities. Subjects will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of AEs. In addition, guidelines for managing AEs, including criteria for treatment discontinuation, are provided below.

**5.1.1**

[Redacted]

[Redacted]

[Redacted]

**5.1.1.1**

[Redacted]

[Redacted]

[Redacted]

**5.1.1.2**

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**5.1.1.3** [Redacted]

[Redacted]

[Redacted]

**5.1.2**      **Management of Toxicities and of Subjects Who Experience Adverse Events**

**5.1.2.1**      **Management Guidelines**

In general, any emerging adverse events must diligently be watched, treated as medically indicated according to common medical practice and documented in terms of onset-date, intensity, off-set date, and any measures taken in order to treat the adverse event.

No specific treatment guidance to any potentially emerging adverse events in balovaptan clinical trials exist and treatment should be according to the common medical practice for the given adverse event.

The Investigator should also consider discontinuation of treatment with balovaptan and itraconazole, in particular, if an adverse event is of severe intensity and considered to be possibly related to balovaptan and itraconazole, respectively.

Temporary dosing interruptions must be discussed with the Sponsor's Medical Monitor in the sense that temporary interruptions will have to be very limited in order to not jeopardize the trial's pharmacokinetic objectives. Dose modifications because of an adverse event are not allowed in this study.

#### 5.1.2.2 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]

[REDACTED]

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[REDACTED]

**5.1.2.3**

[Redacted]

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**5.1.2.4**

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**5.1.2.5**

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**5.1.2.6**

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[REDACTED]

[REDACTED]

**5.2 SAFETY PARAMETERS AND DEFINITIONS**

Safety assessments will consist of monitoring and recording AEs, including SAEs and AEs of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section [5.4](#).



### **5.2.1 Adverse Events**

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.8 for more information)
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (eg, screening invasive procedures such as biopsies)

### **5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)**

An SAE is any AE that meets any of the following criteria:

- Is fatal (ie, the AE actually causes or leads to death)
- Is life threatening (ie, the AE, in the view of the Investigator, places the subject at immediate risk of death)

This does not include any AE that, had it occurred in a more severe form or was allowed to continue, might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.9)
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the Investigator's judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (eg, rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

### **5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)**

Adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below:

Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Clinically relevant decreases in ANC and for which no alternative explanation has been identified (ie, the relationship to study drug is rated "yes")
- CPK values that exceed 10× ULN for several days without a trend of normalization or are associated with relevant dysfunction of kidneys, and if no alternative explanation exists
- Neurological abnormalities emerging from adverse event reporting or neurologic examination that are potentially indicative of dysfunction of peripheral nerves or otherwise represent a neurological deficit and for which no other explanation is apparent
  - Adverse events such as: arrhythmia, syncope, dyspnea, palpitations, or chest pain

## **5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS**

The Investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event Report Form and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4 to 5.6. The Investigator is also responsible for reporting medical device complaints (see Section 5.4.5).

For each AE recorded on the Adverse Event Report Form, the Investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

### **5.3.1 Adverse Event Reporting Period**

Investigators will seek information on AEs at each subject contact. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event Report eCRF (and Form, if appropriate).

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention (eg, invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting SAEs).

After initiation of study drug, all AEs will be reported until up to 21 days after the last dose of study drug.

Instructions for reporting AEs that occur after the AE reporting period are provided in Section 5.6.

### **5.3.2 Eliciting Adverse Event Information**

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all subject evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

### **5.3.3 Assessment of Severity of Adverse Events**

Table 2 provides guidance for assessing AE severity.

**Table 2 Adverse Event Severity Grading Scale**

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of an SAE (see Section 5.2.2).

### **5.3.4 Assessment of Causality of Adverse Events**

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an

AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also [Table 3](#))

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

**Table 3 Causal Attribution Guidance**

Is the AE suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES (RELATED)	There is a plausible temporal relationship between the onset of the AE and administration of the study drug, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO (NOT RELATED)	<u>An AE will be considered related, unless it fulfills the criteria specified below.</u> Evidence exists that the AE has an etiology other than the study drug (eg, pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug (eg, cancer diagnosed 2 days after first dose of study drug).

For subjects receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

### **5.3.5 Procedures for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event Report eCRF (and Form, if appropriate). Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event Report eCRF (and Form, if appropriate).

#### **5.3.5.1 Diagnosis versus Signs and Symptoms**

A diagnosis (if known) should be recorded on the Adverse Event Report eCRF (and Form, if appropriate) rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However,

if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event Report eCRF (and Form, if appropriate). If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

#### **5.3.5.2 Adverse Events That Are Secondary to Other Events**

In general, AEs that are secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event Report eCRF (and Form, if appropriate). For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event Report eCRF (and Form, if appropriate) if it is unclear as to whether the events are associated.

#### **5.3.5.3 Persistent or Recurrent Adverse Events**

A persistent AE is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the Adverse Event Report eCRF (and Form, if appropriate). The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the Adverse Event Report eCRF (and Form, if appropriate). If the event becomes serious, it should be reported to the Sponsor immediately (ie, no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). If a non-serious AE becomes serious, the Investigator will complete the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form and send the form to Roche drug safety. The Adverse Event Report eCRF if already completed should also be updated to serious to correspond with the Adverse Event Reporting Form information sent to drug safety.

A recurrent AE is one that resolves between subject evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event Report eCRF (and Form if appropriate).

#### **5.3.5.4 Abnormal Laboratory Values**

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin  $5 \times$  ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the Adverse Event Report eCRF (and Form if appropriate).

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event Report eCRF (and Form if appropriate), along with a descriptor indicating whether the test result is above or below the normal range (eg, "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event Report eCRF (and Form if appropriate) (see Section 5.3.5.3 for details on recording persistent AEs).

#### **5.3.5.5 Abnormal Vital Sign Values**

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the Adverse Event Report eCRF (and Form if appropriate).

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event Report eCRF (and Form if appropriate)(see Section 5.3.5.3 for details on recording persistent AEs).

#### **5.3.5.6 Abnormal Liver Function Tests**

The finding of an elevated ALT or AST ( $>3 \times \text{ULN}$ ) in combination with either an elevated total bilirubin ( $>2 \times \text{ULN}$ ) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, Investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST  $>3 \times \text{ULN}$  in combination with total bilirubin  $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST  $>3 \times \text{ULN}$  in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event Report eCRF (and Form if appropriate)(see Section 5.3.5.1) and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event), either as an SAE or an AE of special interest (see Section 5.4.2).

#### **5.3.5.7 Deaths**

All deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event Report eCRF and Form and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF and Form. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "**unexplained death**" should be recorded on the Adverse Event eCRF and Form. If the cause of death later becomes available (eg, after autopsy), "unexplained death" should be replaced by the established cause of death. The term "**sudden death**" should not be used unless combined with the presumed cause of death (eg, "sudden cardiac death").



Deaths that occur after the AE reporting period should be reported as described in Section 5.6.

### **5.3.5.8 Pre-existing Medical Conditions**

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF (and Form, if appropriate), it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

### **5.3.5.9 Hospitalization or Prolonged Hospitalization**

Any AE that results in hospitalization (ie, inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or an SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The subject has not experienced an AE

An event that leads to hospitalization under the following circumstances is not considered to be an SAE, but should be reported as an AE instead:

- Hospitalization that was necessary because of subject requirement for outpatient care outside of normal outpatient clinic operating hours



## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious AEs (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Accidental overdoses or medication errors (see Section 5.4.4 for details on reporting requirements)
- Medical device complaints (see Section 5.4.5 for details on reporting requirements)

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (ie, no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and Institutional Review Board/Ethics Committee (IRB/EC).

### 5.4.1 Emergency Medical Contacts

#### **Medical Monitor Contact Information:**

Medical Monitor: [REDACTED], MD (Primary)  
Telephone No.: [REDACTED]  
Mobile Telephone No.: [REDACTED]  
Medical Monitor : [REDACTED], MD (Secondary)  
Telephone No.: [REDACTED]  
Mobile Telephone No.: [REDACTED]

To ensure the safety of study subjects, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls,

provide medical translation service (if necessary), connect the Investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

## **5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest**

### **5.4.2.1 Events That Occur Prior to Study Drug Initiation**

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (ie, no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

### **5.4.2.2 Events That Occur after Study Drug Initiation**

After initiation of study drug, SAEs and adverse events of special interest will be reported until 21 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (ie, within 24 hours after learning of the event) on the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators Adverse Event Report Form and submitting the report, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

Instructions for reporting SAEs that occur 21 days after the last dose of study treatment are provided in Section [5.6](#).

## **5.4.3 Reporting Requirements for Pregnancies**

### **5.4.3.1 Pregnancies in Female Subjects**

Female subjects of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 90 days after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (ie, no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the subject, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (eg, an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF (and Form, if appropriate). In

addition, the Investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### **5.4.3.2 Pregnancies in Female Partners of Male Subjects**

Male subjects will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 90 days after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (ie, no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An Investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

#### **5.4.3.3 Abortions**

Any abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF and Form, and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section [5.4.2](#)).

#### **5.4.3.4 Congenital Anomalies/Birth Defects**

Any congenital anomaly/birth defect in a child born to a female subject exposed to study drug or the female partner of a male subject exposed to study drug should be classified as an SAE, recorded on the Adverse Event Report eCRF and Form, and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section [5.4.2](#)).

#### **5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error**

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves AEs but may result in AEs. All special situations associated with balovaptan, regardless of whether they result in an AE, should be recorded on the Adverse Event Report eCRF and Form and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (eg, wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

For balovaptan and itraconazole, each AE associated with a special situation should be recorded separately on the Adverse Event eCRF and Form. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 5.4.2). For balovaptan, AEs associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the AE term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages and forms, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

#### **5.4.5 Reporting Requirements for Medical Device Complaints**

The Investigator must report all medical device complaints to the Sponsor. The Investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (ie, no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an AE to the study subject, the event must be reported on the Adverse Event eCRF and Form and

submitted through the electronic data capture (EDC) system. If the event is serious, the Adverse Event eCRF and Form must be completed immediately (ie, no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

## **5.5 FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS**

### **5.5.1 Investigator Follow-Up**

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF (and Form, if appropriate) and in the subject's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

### **5.5.2 Sponsor Follow-Up**

For SAEs, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## **5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD**

The Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the end of the AE reporting period (defined in Section 5.3.1) after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event Report Form. The Investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

## **5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES**

The Sponsor will promptly evaluate all SAEs and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference document:

- RO5285119 (Balovaptan) Investigator's Brochure
- Itraconazole Summary of Product Characteristics

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

## **6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN**

A statistical analysis plan will be generated by the biostatistics department of PRA and will be finalized prior to database lock.

### **6.1 DETERMINATION OF SAMPLE SIZE**

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  $AUC_{0-T}$  and 36% for  $C_{max}$  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 SUMMARIES OF CONDUCT OF STUDY**

The number of subjects who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

### **6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS**

Demographic and baseline characteristics will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment.

### **6.4 EFFICACY ANALYSES**

Not applicable.

## 6.5 SAFETY ANALYSES

All subjects who have received at least one dose of balovaptan, whether prematurely withdrawn from the study or not, will be included in the safety analysis.

The safety data, including AEs, laboratory data, and vital signs, will be listed and summarized by treatment. Reasons for withdrawal from study will be listed and summarized. Concomitant medications, 12-lead ECG data, and clinically significant neurological examinations will be listed.

Adverse events will be listed and summarized by treatment, body system and preferred term using the Medical Dictionary for Regulatory Activities. All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to [Table 2](#).

For laboratory and 12-lead ECG data, subject listings will be presented with abnormalities flagged.

## 6.6 PHARMACOKINETIC ANALYSES

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 together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

Individual plasma concentrations at each sampling timepoint for balovaptan, M2 (as applicable), M3, itraconazole and hydroxy-itraconazole will be presented by listings and descriptive summary statistics by treatment, including means, geometric means, ranges, standard deviations and coefficients of variation. Individual and mean concentration versus time will be plotted on linear and semi-logarithmic scales.

All PK parameters for balovaptan, M2 (as applicable), and M3 will be presented by individual listings and summary statistics by treatment including means, geometric means, medians, ranges, standard deviations and coefficients of variation.

The following balovaptan PK parameters will be estimated:

- $C_{max}$ : Day 10 of Period 1; Day 15 and Day 20 of Period 2
- $AUC_{0-T}$ : Day 10 of Period 1; Day 15 and Day 20 of Period 2
- $T_{max}$ : Day 10 of Period 1; Day 15 and Day 20 of Period 2
- $C_{trough}$ : Day 10 of Period 1; Day 15 and Day 20 of Period 2)
- time to steady state (for balovaptan)

The primary PK parameters are  $C_{max}$  and  $AUC_{0-T}$  for balovaptan, M2, and M3 on Day 10 of Period 1 and Day 20 of Period 2.

A linear mixed model analysis will be applied to analyze the log-transformed primary PK parameters. The model assumes a fixed effect for treatment and a random effect for subject. Estimates of geometric mean ratios together with the corresponding 90% CIs will be derived for the comparisons of the PK parameters as follows:

- balovaptan plus itraconazole (test) vs balovaptan alone (reference)

For itraconazole and hydroxy-itraconazole,  $C_{max}$ ,  $AUC_{0-24h}$ , and  $T_{max}$  will be estimated on Day 5 and Day 20 to evaluate whether adequate levels were reached.

Additional PK parameters may be derived if deemed necessary.

## **6.7 OTHER ANALYSES**

### **6.7.1 Genotyping**

The relationship between CYP3A4 genotype and steady state balovaptan exposure and the influence of CYP3A4 genotype on the effect of itraconazole on balovaptan PK and CYP3A enzyme activity will be evaluated. Other isoforms may also be analysed.

## **6.8 INTERIM ANALYSES**

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.

## **7. DATA COLLECTION AND MANAGEMENT**

### **7.1 DATA QUALITY ASSURANCE**

The Sponsor will supply eCRF specifications for this study. The contract research organization (CRO), PRA Health Sciences (PRA), will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, PRA will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

PRA will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to PRA using PRA's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the PRA's data management plans and specifications. Data will be periodically transferred electronically from PRA to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.



Electronic case report forms and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

## **7.2 ELECTRONIC CASE REPORT FORMS**

Electronic case report forms are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. Electronic case report forms should be reviewed and electronically signed and dated by the Investigator or a designee.

At the end of the study, the Investigator will receive subject data for his or her site in a readable format on a compact disc that must be kept with the study records.

Acknowledgement of receipt of the compact disc is required.

## **7.3 ELECTRONIC PATIENT-REPORTED OUTCOME**

Not applicable.

## **7.4 SOURCE DATA DOCUMENTATION**

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (ie, source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which subject data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (ie, no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section [7.6](#).

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

## **7.5 USE OF COMPUTERIZED SYSTEMS**

When clinical observations are entered directly into a study site's computerized medical record system (ie, in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

## **7.6 RETENTION OF RECORDS**

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper patient-reported outcome data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

## **8. ETHICAL CONSIDERATIONS**

### **8.1 COMPLIANCE WITH LAWS AND REGULATIONS**

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a US Investigational New Drug (IND) Application will comply with US Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU) or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

## **8.2 INFORMED CONSENT**

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The Investigator or authorized designee will explain to each subject the objectives, methods, and potential risks associated with each optional procedure. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a subject's agreement to participate in optional procedures. Subjects who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the subject or the subject's legally authorized representative before his or her participation in the study. The case history or clinical records for each subject shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the subject to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Subjects must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each subject shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the subject or the subject's legally authorized representative. All signed and dated Consent Forms must remain in each subject's study file or in the site file and must be available for verification by study monitors at any time.

## **8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE**

This protocol, the Informed Consent Forms, any information to be given to the subject, and relevant supporting information must be submitted to the IRB/EC by the Principal

Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any subject recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

#### **8.4 CONFIDENTIALITY**

The Sponsor maintains confidentiality standards by coding each subject enrolled in the study through assignment of a unique subject identification number. This means that subject names are not included in data sets that are transmitted to any Sponsor location.

Subject medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the subject, unless permitted or required by law.

Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or subjects unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

#### **8.5 FINANCIAL DISCLOSURE**

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the

course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

## **9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION**

### **9.1 STUDY DOCUMENTATION**

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the Investigator will receive the subject data, including an audit trail containing a complete record of all changes to data.

### **9.2 PROTOCOL DEVIATIONS**

The Investigator should document and explain any protocol deviations. The Investigator should promptly report any deviations that might have an impact on subject safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

### **9.3 SITE INSPECTIONS**

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The Investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

### **9.4 ADMINISTRATIVE STRUCTURE**

The Sponsor of the trial is F. Hoffmann-La Roche Ltd. The Sponsor has contracted PRA, who will be delegated responsibility for various aspects of this clinical trial.

One site will participate to enroll 14 to 18 subjects.

Central facilities will be used for certain study assessments throughout the study (eg, specified laboratory tests and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

### **9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS**

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific

congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

[www.roche.com/roche\\_global\\_policy\\_on\\_sharing\\_of\\_clinical\\_study\\_information.pdf](http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf)

The results of this study may be published or presented at scientific congresses. For all clinical trials in subjects involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in subjects involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

## **9.6 PROTOCOL AMENDMENTS**

Any protocol amendments will be prepared by PRA. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects or changes that involve logistical or administrative aspects only (eg, change in Medical Monitor or contact information).

## 10. REFERENCES

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## Appendix 1 Schedule of Activities

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	
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 <sup>a</sup>	X																								
Pregnancy test <sup>b</sup>	X	X							X																X
Balovaptan administration <sup>c</sup>			X	X	X	X								X	X	X	X	X	X	X	X	X	X		
PK sampling for Balovaptan and metabolites M2 and M3 <sup>d</sup>			X	X	X	X	X							X		X	X	X	X	X	X	X	X		
Itraconazole administration <sup>e</sup>									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PK sampling for Itraconazole and hydroxyl-itraconazole <sup>f</sup>														X	X <sup>n</sup>						X	X			
Genotyping sample		X																							
Physical examination	X								X														X <sup>g</sup>	X	
Height, body weight and BMI <sup>h</sup>	X	X							X																





## Appendix 1 Schedule of Activities (cont.)

<sup>i</sup>See [Appendix 2](#) for specific ECG time points by study day

<sup>j</sup>See [Appendix 2](#) for specific vital signs time points by study day

<sup>k</sup>Prior to breakfast

<sup>l</sup>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

<sup>m</sup>Predose

<sup>n</sup>Assessments performed on Days 6, 8, and 10

<sup>o</sup>Assessments performed on Day 17

<sup>p</sup>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 2

### Schedule of Pharmacokinetic Sampling, Electrocardiogram, 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													
<i>Period 1</i>													
Day 1, 3, 5, 8, 9	X <sup>a</sup>												
Day 10	X <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X <sup>b</sup>	X <sup>b</sup>
<i>Period 2</i>													
Day 6, 8, 10, 13, 14, 16, 18, 19	X <sup>a</sup>												
Day 15	X <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X <sup>c</sup>	X <sup>c</sup>
Day 20	X <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X <sup>d</sup>	X <sup>d</sup>
Blood sampling itraconazole and hydroxyl-itraconazole													
<i>Period 2</i>													
Day 5	X <sup>a</sup>		X		X				X				
Day 6, 8, 10, 14, 15, 16, 18, 19	X <sup>a</sup>												
Day 20	X <sup>a</sup>		X		X				X				X <sup>c</sup>
12-lead electrocardiograms													
<i>Period 1</i>													
Days 1 and 10	X												
<i>Period 2</i>													
Day 1	X <sup>e</sup>												
Day 5, 6, 8, 10, 13, 15, 17, 20	X				X								
Vital signs													
<i>Period 1</i>													
Day 1	X												
Day 11 <sup>f</sup>													
<i>Period 2</i>													

## Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

Procedure Study Day	Predose	Hours post dose										
		1	2	3	4	5	6	8	10	12	16	24
Day 1	X <sup>e</sup>											
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 <sup>f</sup>												

<sup>a</sup>10 minutes predose (or time matched, when not dosed)

<sup>b</sup>Day 11

<sup>c</sup>Day 16

<sup>d</sup>Day 21

<sup>e</sup>Pre-AM dose

<sup>f</sup>Prior to discharge