

Official Title: A SINGLE-CENTER, NON-RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, TWO-TREATMENT STUDY INVESTIGATING THE ABSOLUTE ORAL BIOAVAILABILITY OF BALOVAPTAN AFTER SINGLE AND MULTIPLE DAILY ORAL 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

DATE FINAL: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name

[REDACTED]

Title

Company Signatory

Date and Time (UTC)


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PROTOCOL ACCEPTANCE FORM

TITLE: A SINGLE-CENTER, NON-RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, TWO-TREATMENT STUDY INVESTIGATING THE ABSOLUTE ORAL BIOAVAILABILITY OF BALOVAPTAN AFTER SINGLE AND MULTIPLE DAILY ORAL DOSES OF BALOVAPTAN IN HEALTHY VOLUNTEERS

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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.

[REDACTED]
Roche Products Limited
6 Falcon Way, Shire Park
Welwyn Garden City,
AL7 1TW, United Kingdom

PROTOCOL SYNOPSIS

TITLE: A SINGLE-CENTER, NON-RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, TWO-TREATMENT STUDY INVESTIGATING THE ABSOLUTE ORAL BIOAVAILABILITY OF BALOVAPTAN AFTER SINGLE AND MULTIPLE DAILY ORAL DOSES OF BALOVAPTAN IN HEALTHY VOLUNTEERS

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IND NUMBER: NA

TEST PRODUCT: Balovaptan (RO5285119)

PHASE: I

INDICATION: Not applicable

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the PK of balovaptan. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
<ul style="list-style-type: none"> To determine the absolute oral bioavailability of a single dose of 10 mg balovaptan. 	<ul style="list-style-type: none"> Absolute bioavailability (F) for balovaptan at the indicated dose level.
Secondary Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To determine the absolute oral bioavailability of a single dose of 50 mg balovaptan. To determine the absolute oral bioavailability of balovaptan after once daily doses of 10 mg or 50 mg for 14 days. To characterize the dose- and time-dependency of the PK of oral balovaptan. To determine plasma concentrations of [¹³C]-labeled balovaptan, balovaptan, and its metabolites M2, and M3, following a single oral dose of balovaptan 10 mg or 50 mg together with a slow IV infusion of a microdose of [¹³C]-labeled balovaptan. To determine plasma concentrations of [¹³C]-labeled balovaptan, balovaptan, and its metabolites M2, and M3, following once daily oral dosing of 10 mg or 50 mg QD for 14 days together with a slow IV infusion of a microdose of [¹³C]-labeled balovaptan after the last oral dose. 	<ul style="list-style-type: none"> Absolute bioavailability (F) for balovaptan at the indicated dose level. Plasma concentrations and associated PK parameters for [¹³C]-labeled balovaptan, balovaptan, and its metabolites M2, and M3, including but not limited to C_{max}, t_{max}, t_{1/2}, AUC_{last}, AUC_{inf}, AUC₀₋₂₄, C_{last}, t_{last}, λ_z, and (for [¹³C]-parent only) CL on Day 1 and Day 14 and V_{ss} on Day 1 and Day 14.
<ul style="list-style-type: none"> To evaluate the safety and tolerability of balovaptan 10 mg QD and 50 mg QD 	<ul style="list-style-type: none"> Adverse events (AEs), clinical laboratory values, vital signs, electrocardiogram (ECG), and physical examination
Exploratory Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To determine whether genes relating to drug-metabolizing enzymes and/or drug transporter enzymes affect the PK and/or the safety profile of balovaptan. 	<ul style="list-style-type: none"> The pharmacogenetics^a of metabolizing enzymes, transferases, transporters, etc., possibly involved in the absorption, distribution, metabolism and excretion of balovaptan and its major metabolites (e.g., CYP3A and P-glycoprotein).
<ul style="list-style-type: none"> [REDACTED] 	<ul style="list-style-type: none"> [REDACTED]

AE = adverse events; [REDACTED]; CYP = cytochrome P450; DNA = deoxyribonucleic acid; ECG = electrocardiogram; F = bioavailability; IV = intravenous; PK = pharmacokinetic; QD = once daily

^a Results may be pooled with data from other studies of balovaptan and will be reported separately.

Study Design

Description of Study

This study will be a non-randomized, open-label, parallel group, two-treatment study in healthy volunteers to investigate the absolute oral bioavailability of balovaptan. The study will be conducted at 1 site in the Netherlands.

Screening will be conducted up to 28 days prior to admission to the clinical research unit (CRU).

Subjects will be in the CRU for 2 study periods. In both periods, subjects will be admitted on Day -1 (the day before dosing begins). Day 1 will be the first day of dosing. In Period 1, subjects will be discharged on Day 10 after all assessments have been completed. There will be a wash-out period of 14 days between Day 1 of Period 1 and Day 1 of Period 2.

Subjects will be readmitted to the CRU for a second in-house period on Day 14 of Period 1 (Day -1 of Period 2) to begin Period 2. Day 1 will be the first day of dosing. In Period 2, subjects will be discharged in the morning of Day 19.

During the in-house stays and screening and follow-up visits, subjects will undergo assessments of AEs and concomitant medications, vital signs, electrocardiograms (ECGs), clinical laboratory evaluations, and blood sampling for PK evaluations. [REDACTED]

Dosing

Two cohorts of 8 subjects each will be included in the study. The 2 cohorts will receive the following treatment regimens:

Cohort 1

Period 1:

- Day 1: a single oral dose of 10 mg balovaptan after at least 10 hours of fasting, followed 1.25 hours later by a 15-minute intravenous (IV) infusion of [¹³C]-labeled balovaptan 0.1 mg.

Period 2:

- Day 1 to Day 14: oral doses of 10 mg balovaptan QD; on Day 7 and Day 14 study drug administration will take place after at least 10 hours of fasting.
- Day 14: the final oral dosing will be followed 1.25 hours later by a 15-minute IV infusion of [¹³C]-labeled balovaptan 0.1 mg.

Cohort 2

Period 1:

- Day 1: a single oral dose of 50 mg balovaptan after at least 10 hours of fasting, followed 1.25 hours later by a 15-minute IV infusion of [¹³C]-labeled balovaptan 0.1 mg.

Period 2:

- Day 1 to Day 14: oral doses of 50 mg balovaptan QD; on Day 7 and Day 14 study drug administration will take place after at least 10 hours of fasting.
- Day 14: the final oral dosing will be followed 1.25 hours later by a 15-minute IV infusion of [¹³C]-labeled balovaptan 0.1 mg.

Subjects will return for a follow-up visit between 14 and 21 days after the last dose. Follow-up visit will include a physical examination (excluding height), routine safety laboratory tests, 12-lead ECG (single) and vital signs (systolic and diastolic blood pressure and pulse rate).

Number of Subjects

A total of 8 subjects per cohort will be enrolled with the target of at least 6 subjects available for the primary PK analysis.

Target Population

The target population will be healthy male (at least 4 male subjects enrolled per cohort) and female subjects, aged 18 to 65 years, inclusive, at screening. At least 4 subjects enrolled per cohort should be aged 18 to 50 years, inclusive, at screening.

Inclusion Criteria

Subjects must meet the following criteria for study entry:

1. Healthy male or female subject, 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/m², 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. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.
 - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 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 (IUD); copper IUD; 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.

Exclusion Criteria

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

1. Female subjects who are pregnant or lactating.
2. If female of childbearing potential, a positive serum pregnancy test at screening or at admission to the CRU (Day -1 of each period).
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, 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 (e.g., to drugs, including 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 milliseconds [msec] or <300 msec (using the same upper QTcF limit in both males and females).
 12. Notable resting bradycardia (mean heart rate [HR] <40 beats per minute [bpm]) on screening or predose baseline ECG. Notable resting tachycardia on screening (mean HR > 90 bpm) or predose (mean HR > 100 bpm) baseline ECG.
 13. Screening or baseline ECGs with QRS and/or T-wave judged to be unfavorable for a consistently accurate QT measurement (i.e., 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. Systolic blood pressure greater than 139 or less than 90 mmHg, or diastolic blood pressure greater than 89 or less than 45 mmHg, based on the average of ≥ 3 consecutive measurements.
 16. Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel, coagulation parameters, 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.
 17. History of coagulopathies, bleeding disorders, or blood dyscrasias.
 18. Subjects who have smoked within 3 months prior to first dose administration.
 19. 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.
 20. 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 1/6 gill (25 mL) of spirits.
 21. Positive urine alcohol test or urine drug screen at screening or each admission (Day -1 of each period) (barbiturates, benzodiazepines, methadone, amphetamines [including ecstasy], methamphetamines, opiates, cocaine, and cannabinoids).
 22. Positive result on human immunodeficiency virus (HIV)-1, HIV-2 antibodies, hepatitis C virus (HCV) antibody, hepatitis B virus surface antigen (HBsAg), or hepatitis B core (HepBc) antibody screen.
 23. 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.
 24. Any donation of blood or plasma or significant blood loss within 3 months prior to screening.
 25. Dietary restrictions that would prohibit the consumption of standardized meals.
 26. Use of any prohibited medications OR food before study start OR subjects who do not agree to refrain from consuming prohibited medications or food during the study.

27. Subjects likely to need concomitant medication during the study (including for dental conditions).
 28. Subjects who have received any prescribed systemic or topical medication within 4 weeks (or within 5 times the elimination half-life of the medication, whichever is longer) 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 4 weeks (or within 5 times the elimination half-life of the medication, whichever is longer) 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.
 29. 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 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.
30. 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.
 31. 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.
 32. Subjects under judicial supervision, guardianship or curatorship.
 33. Poor venous access for blood sampling.
 34. Subjects who have previously taken part in or withdrawn from this study.
 35. Subjects who are unwilling to practice safe sex (use male or female condom) for the duration of the study.
 36. [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 37. Significant risk for suicidal behavior, in the opinion of the Investigator.

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.

Length of Study

The end of the study is expected to occur approximately 12 weeks after the last subject is enrolled, but this may be longer if, for example, subjects need to be replaced. 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

RO5285119/F17 10 mg dispersible film-coated tablets will be supplied by the Sponsor in high density polyethylene bottles. For information on the formulation and handling of balovaptan, see the Investigational Medicinal Product Dossier.

[¹³C]-Labeled Balovaptan

The [¹³C]-labeled balovaptan drug substance will be supplied by the Sponsor. RO5285119/F40 [¹³C]-labeled balovaptan solution (20 µg/ml) for IV infusion will be prepared by the site. For information on the formulation and handling of [¹³C]-labeled balovaptan, see the Investigational Medicinal Product Dossier.

Statistical Methods

Primary Analysis

The primary PK parameter is absolute bioavailability (F) for balovaptan following a single 10 mg dose.

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 the absolute bioavailability of the 10 mg single dose with sufficient precision.

A total of 8 subjects per cohort are to be enrolled with the target of at least 6 subjects available for the primary PK analysis (i.e., having taken a single dose of 10 mg on Day 1 and completed all PK assessment up to Day 10). If the number of subjects providing PK data from the multiple dose parts of the study is lower than 6 for either cohort more subjects may be enrolled.

Assuming a within-subject variability of around 35% it can be estimated that with 6 subjects the half-width of the 90% confidence interval (CI) for the ratio of geometric means of the microdose IV kinetics with that from the oral dose (i.e. CL versus CL/F) would be obtained by dividing/multiplying the ratio estimate by a factor of 1.50.

The within-subject variability value of around 35% has been identified as a reasonable assumption: it is smaller than the observed 42% between-subject variability for the apparent clearance of distribution (CL/F) from a single oral 10 mg dose in study WP40038, and it considers that the reference will be obtained from IV kinetics, which is expected to be less variable than oral kinetics.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
λ_z	terminal elimination rate constant
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated thromboplastin time
ASD	autism spectrum disorder
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve over the dosing interval at steady state
AUC_{0-120h}	area under the plasma concentration vs time curve from time zero to 120 hours
AUC_{inf}	area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to the last measurable plasma concentration time point
BMI	body mass index
bpm	beats per minute
C-SSRS	Columbia-Suicide Severity Rating Scale
CI	confidence interval
CL	total body clearance
C_{last}	last measurable plasma concentration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
CRO	contract research organization
CRU	clinical research unit
████	████████████████████
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form

EDC	electronic data capture
EU	European Union
F	absolute bioavailability
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HepBc	hepatitis B core
hERG	human ether-à-go-go related gene
HR	heart rate
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IC20	20% inhibition
IMP	investigational medicinal product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
λ_z	terminal elimination rate constant
LC/MS/MS	liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond(s)
NOEL	no observed effect level
NOAEL	no observed adverse effect level
NCI	National Cancer Institute
NT-proBNP	N-terminal pro B-type natriuretic peptide
P-gp	P-glycoprotein
PK	pharmacokinetic
PND	postnatal day
PRA	PRA Health Sciences

QD	once daily
QTcF	QT interval corrected through use of Fridericia's formula
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOP	standard operating procedure
$t_{1/2}$	apparent terminal half-life
t_{last}	time of last measurable plasma concentration
t_{max}	time to maximum observed plasma concentration
ULN	upper limit of normal
US	United States
V1a	vasopressin receptor 1A
V_{ss}	volume of distribution
WBC	white blood cell

1. **BACKGROUND**

1.1 **AUTISM SPECTRUM DISORDER**

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by 2 core domains: impairments in social interaction and communication and 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's records, that the estimated prevalence of ASD in the United States (US) 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 comorbid conditions, including irritability, depression or anxiety, attention deficits, obsessive compulsive symptoms, seizures, and sleep disruption. Functional and structural deficits in the brain network subserving the processing of social cues (such as faces and speech) and social affiliative behavior have 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, and currently available treatments address only associated behavioral problems. 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 large 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 the neuropsychiatric disorder most affected by genetic factors. The vasopressin system has been implicated in autism by studies of the arginine vasopressin receptor 1A (V1a) gene, which encodes 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 ribonucleic acid (RNA) levels in the human hippocampus post-mortem. In particular, both nonclinical and clinical research support a specific role for 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. Given 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.

[REDACTED]

[REDACTED]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[REDACTED]

1.2.1 Previous and Ongoing Clinical Studies

To date, balovaptan has been investigated in 6 completed Phase 1 studies including a proof-of-mechanism study in healthy volunteers (Study BP29412). Two Phase 1 studies (Study WP40608, drug-drug interaction [DDI] study with rifampicin and Study WP40609, DDI study with itraconazole) are ongoing.

A Phase 2 study in adult male ASD patients has been completed (Study BP28420, also referred to as VANILLA). A Phase 2 study in pediatric ASD patients (Study BP30153, also referred to as AV1ATION) and a Phase 3 study in adult ASD patients (Study WN39434, also known as V1aduct) are ongoing in both male and female patients.

1.2.1.1 Clinical Pharmacology

Plasma 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 in fasted state and between 3 and 4 hours following multiple dosing in fed state. Steady state was achieved after approximately 7 days, with an accumulation of approximately 4-fold after 12 mg QD and 2-fold after 52 mg QD; the mean apparent elimination half-life after the last dose (Day 14) was approximately 46 hours. Food had no relevant effect on the overall plasma area under the plasma concentration-time curve (AUC) 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.

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]

[REDACTED]

[REDACTED]

[REDACTED]

Hepatic metabolism was found to be the major pathway of elimination with the primary route of excretion via urine (approximately 53% of the material recovered, mostly

composed of metabolites). A further 30% of the administered dose was recovered in feces. The majority of excretion occurred within the first 7 days.

There was no clinically/statistically relevant PK interaction with the P-gp 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 36% for maximum observed plasma concentration (C_{max}) and an approximately 3.1-fold increase for area under the concentration curve from time 0 to 120 hours (AUC_{0-120h}).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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. The primary objective in this study is to assess the absolute oral bioavailability of a single dose of 10 mg balovaptan. (see also Section 3.3). In addition, as the PK of balovaptan may be time and dose-dependent, the bioavailability will be tested at steady state and at a higher dose level (50 mg).

To date, balovaptan has been dosed to 209 healthy subjects in 6 completed Phase 1 studies (Studies BP25694, BP28318, BP28977, BP29279, BP29412, and WP40038).

Additionally, balovaptan was dosed to 148 adult male patients with ASD in the completed Phase 2 study BP28420 (“VANILLA”), about 30 of whom received 10 mg QD for 12 weeks.

[REDACTED]

[REDACTED]

In this study WP40607, multiple doses of 10 mg or 50 mg QD balovaptan will be administered to healthy volunteers for no longer than 14 days. While planned dosing of subjects in this study has been shown to be safe and well tolerated in previous Clinical Pharmacology trials, diligent safety monitoring and in-house stays are included in this study during dosing. Subjects will be asked to report any events of feeling “not well” to study staff immediately.

[REDACTED]

The safety plan is detailed in Section 5.1.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the PK of balovaptan. [Table 1](#) presents objectives and endpoints.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
<ul style="list-style-type: none"> To determine the absolute oral bioavailability of a single dose of 10 mg balovaptan. 	<ul style="list-style-type: none"> Absolute bioavailability (F) for balovaptan at the indicated dose level.
Secondary Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To determine the absolute oral bioavailability of a single dose of 50 mg balovaptan. To determine the absolute oral bioavailability of balovaptan after once daily doses of 10 mg or 50 mg for 14 days. To characterize the dose- and time-dependency of the PK of oral balovaptan. To determine plasma concentrations of [¹³C]-labeled balovaptan, balovaptan, and its metabolites M2, and M3, following a single oral dose of balovaptan 10 mg or 50 mg together with a slow IV infusion of a microdose of [¹³C]-labeled balovaptan. To determine plasma concentrations of [¹³C]-labeled balovaptan, balovaptan, and its metabolites M2, and M3, following once daily oral dosing of 10 mg or 50 mg QD for 14 days together with a slow IV infusion of a microdose of [¹³C]-labeled balovaptan after the last oral dose. 	<ul style="list-style-type: none"> Absolute bioavailability (F) for balovaptan at the indicated dose level. Plasma concentrations and associated PK parameters for [¹³C]-labeled balovaptan, balovaptan, and its metabolites M2, and M3, including but not limited to C_{max}, t_{max}, t_{1/2}, AUC_{last}, AUC_{inf}, AUC₀₋₂₄, C_{last}, t_{last}, λ_z, and (for [¹³C]-parent only) CL on Day 1 and Day 14 and V_{ss} on Day 1 and Day 14.
<ul style="list-style-type: none"> To evaluate the safety and tolerability of balovaptan 10 mg QD and 50 mg QD 	<ul style="list-style-type: none"> Adverse events (AEs), clinical laboratory values, vital signs, electrocardiogram (ECG), and physical examination
Exploratory Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To determine whether genes relating to drug-metabolizing enzymes and/or drug transporter enzymes affect the PK and/or the safety profile of balovaptan. 	<ul style="list-style-type: none"> The pharmacogenetics^a of metabolizing enzymes, transferases, transporters, etc., possibly involved in the absorption, distribution, metabolism and excretion of balovaptan and its major metabolites (e.g., CYP3A and P-glycoprotein).
<ul style="list-style-type: none"> [REDACTED] 	<ul style="list-style-type: none"> [REDACTED]

AE = adverse events; [REDACTED]; CYP = cytochrome P450; DNA = deoxyribonucleic acid; ECG = electrocardiogram; F = bioavailability; IV = intravenous; PK = pharmacokinetic; QD = once daily

^a Results may be pooled with data from other studies of balovaptan and will be reported separately.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This study will be a non-randomized, open-label, parallel group, two-treatment study in healthy volunteers to investigate the absolute oral bioavailability of balovaptan. The study will be conducted at 1 site in the Netherlands.

Screening

Screening will be conducted up to 28 days prior to admission to the clinical research unit (CRU).

In-Clinic Confinement

Subjects will be in the CRU for 2 study periods. In both periods, subjects will be admitted on Day -1 (the day before dosing begins). Day 1 will be the first day of dosing. In Period 1, subjects will be discharged on Day 10 after all assessments have been completed. There will be a wash-out period of 14 days between Day 1 of Period 1 and Day 1 of Period 2.

Subjects will be readmitted to the CRU for a second in-house period on Day 14 of Period 1 (Day -1 of Period 2) to begin Period 2. Day 1 will be the first day of dosing. In Period 2, subjects will be discharged in the morning of Day 19.

During the in-house stays and screening and follow-up visits, subjects will undergo assessments as outlined in the schedule of activities ([Appendix 1](#)), including assessments of AEs and concomitant medications, vital signs, electrocardiograms (ECGs), clinical laboratory evaluations, and blood sampling for PK evaluations. ■

Dosing

Two cohorts of 8 subjects each will be included in the study. The 2 cohorts will receive the following treatment regimens:

Cohort 1

Period 1:

- Day 1: a single oral dose of 10 mg balovaptan after at least 10 hours of fasting, followed 1.25 hours later by a 15-minute intravenous (IV) infusion of [¹³C]-labeled balovaptan 0.1 mg.

Period 2:

- Day 1 to Day 14: oral doses of 10 mg balovaptan QD; on Day 7 and Day 14 study drug administration will take place after at least 10 hours of fasting.
- Day 14: the final oral dosing will be followed 1.25 hours later by a 15-minute IV infusion of [¹³C]-labeled balovaptan 0.1 mg.

Cohort 2

Period 1:

- Day 1: a single oral dose of 50 mg balovaptan after at least 10 hours of fasting, followed 1.25 hours later by a 15-minute IV infusion of [¹³C]-labeled balovaptan 0.1 mg.

Period 2:

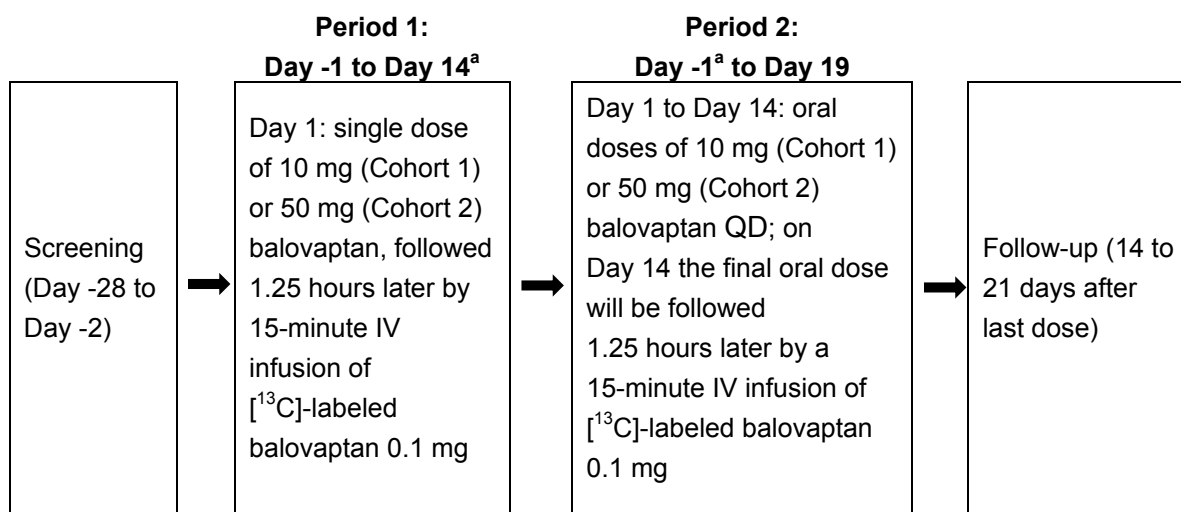
- Day 1 to Day 14: oral doses of 50 mg balovaptan QD; on Day 7 and Day 14 study drug administration will take place after at least 10 hours of fasting.
- Day 14: the final oral dosing will be followed 1.25 hours later by a 15-minute IV infusion of [¹³C]-labeled balovaptan 0.1 mg.

Follow-up

Subjects will return for a follow-up visit between 14 and 21 days after the last dose. Follow-up visit will include a physical examination (excluding height), routine safety laboratory tests, 12-lead ECG (single) and vital signs (systolic and diastolic blood pressure and pulse rate).

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

Figure 1 Study Schema



IV = intravenous; QD = once daily

^a Day 14 of Period 1 is Day -1 of Period 2

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 occurs, or safety follow-up is received from the last subject, whichever occurs later. The end of the

study is expected to occur approximately 12 weeks after the last subject is enrolled, but this may be longer if, for example, subjects need to be replaced.

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 the absolute oral bioavailability of a single dose of 10 mg balovaptan. The secondary objectives are also PK objectives. 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 bioavailability studies with an open-label design, without placebo treatments, and since evaluation of safety and tolerability is not a primary objective of this study, an open-label design was deemed appropriate.

3.3.2 Rationale for Balovaptan Dose and Schedule

A dose of 10 mg balovaptan has shown statistically significant changes in efficacy parameters in patients with ASD and is the current recommended Phase 3 dose.

In addition, a dose of 50 mg balovaptan will be studied as well to investigate any dose-dependent changes in oral bioavailability. In the MAD part of study BP25694, multiple doses of 52 mg QD in healthy subjects were well tolerated and resulted in a C_{max} of 484 ng/mL, [REDACTED]. Thus, a dose of 50 mg balovaptan QD is considered suitable to study dose-dependent changes in oral bioavailability.

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-dependent. Accumulation was observed with multiple dosing, and steady state of balovaptan was observed after approximately 7 days of dosing and after 10 days for M3. The plasma PK time course of M2 has not been closely studied but steady state has been demonstrated after 2 weeks of QD dosing with balovaptan 10 mg. Based on these observations, a dosing period of 14 days has been selected to ensure steady state plasma levels of balovaptan and its major metabolites M2 and M3 are reached and to maximize the possibility to observe any time-dependent changes in PK.

The microdose of [¹³C]-labeled balovaptan has been set to 0.1 mg; 0.1 mg is the maximum allowed IV microdose that can be administered without IV toxicity studies. Exposure after an 0.1-mg IV dose is covered by the existing nonclinical toxicity and PK

data. The t_{max} following oral dosing in the fasted state is expected to be approximately 1.5 hours postdose after a single dose and approximately 3 hours after multiple doses. To have the end of the infusion and the t_{max} of [^{13}C]-labeled balovaptan coincide with the t_{max} of the orally administered unlabeled balovaptan after a single dose, the 15-minute infusion of the microdose of [^{13}C]-labeled balovaptan will be started at 1.25 hours. For consistency the time of infusion is similar after the (last) multiple oral dose when due to accumulation plasma levels of balovaptan are predicted to not be lower than at t_{max} after the single dose.

3.3.3 Rationale for Study Population

Healthy male or female volunteers aged 18 to 65 years inclusive 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.

Although volunteers aged 18 to 65 years inclusive may be included in the study, a minimum of 4 subjects per cohort have to be aged 18 to 50 years inclusive. This is considered desirable because the observation of dose-dependency of PK was made in previous studies enrolling volunteers aged 18 to 50 years inclusive, and is expected to ensure comparability of this study WP40607 to previous studies. In addition, a minimum of 4 subjects per cohort will be male, as ASD male patients will be the main target population for balovaptan.

[REDACTED]

3.3.5 Rationale for Genomics Assessments

A blood sample for DNA extraction will be taken from every participant on Day -1 of Period 1. The DNA will be used to evaluate if genes relating to drug-metabolizing enzymes and/or drug transporter enzymes affect the PK and/or the safety profile of balovaptan.

Data may be analyzed in the context of this study but will also be explored in aggregate with data from other studies.

4. MATERIALS AND METHODS

4.1 SUBJECTS

The target population will be healthy male (at least 4 male subjects enrolled per cohort) and female subjects, aged 18 to 65 years, inclusive, at screening. At least 4 subjects enrolled per cohort should be aged 18 to 50 years, inclusive, at screening.

A total of 8 subjects per cohort will be enrolled with the target of at least 6 subjects available for the primary PK analysis (i.e., having taken a single dose of balovaptan on Day 1 and completed all PK assessments up to Day 10). If the number of subjects providing PK data from the single or multiple dose parts of the study is lower than 6 for either cohort, more subjects may 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 or female subject, 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/m², 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. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.
 - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 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 (IUD); copper IUD; 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 pregnant or lactating.
2. If female of childbearing potential, a positive serum pregnancy test at screening or at admission to the CRU (Day -1 of each period).
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, 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 (e.g., to drugs, including 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 milliseconds [msec] or <300 msec (using the same upper QTcF limit in both males and females).
12. Notable resting bradycardia (mean HR <40 beats per minute [bpm]) on screening or predose baseline ECG. Notable resting tachycardia on screening (mean HR > 90 bpm) or predose (mean HR > 100 bpm) baseline ECG.
13. Screening or baseline ECGs with QRS and/or T-wave judged to be unfavorable for a consistently accurate QT measurement (i.e., 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. Systolic blood pressure greater than 139 or less than 90 mmHg, or diastolic blood pressure greater than 89 or less than 45 mmHg, based on the average of ≥ 3 consecutive measurements.
16. Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel, coagulation parameters, 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.
17. History of coagulopathies, bleeding disorders, or blood dyscrasias.
18. Subjects who have smoked within 3 months prior to first dose administration.
19. 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.
20. 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.
21. Positive urine alcohol test or urine drug screen at screening or each admission (Day -1 of each period) (barbiturates, benzodiazepines, methadone, amphetamines [including ecstasy], methamphetamines, opiates, cocaine, and cannabinoids).
22. Positive result on human immunodeficiency virus (HIV)-1, HIV-2 antibodies, hepatitis C virus (HCV) antibody, hepatitis B virus surface antigen (HBsAg), or hepatitis B core (HepBc) antibody screen.
23. 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.
24. Any donation of blood or plasma or significant blood loss within 3 months prior to screening.

25. Dietary restrictions that would prohibit the consumption of standardized meals.
26. Use of any prohibited medications OR food before study start OR subjects who do not agree to refrain from consuming prohibited medications or food during the study (see Section 4.4).
27. Subjects likely to need concomitant medication during the study (including for dental conditions).
28. Subjects who have received any prescribed systemic or topical medication within 4 weeks (or within 5 times the elimination half-life of the medication, whichever is longer) 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 4 weeks (or within 5 times the elimination half-life of the medication, whichever is longer) 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.
29. 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 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.

30. 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.
31. 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.
32. Subjects under judicial supervision, guardianship or curatorship.
33. Poor venous access for blood sampling.
34. Subjects who have previously taken part in or withdrawn from this study.
35. Subjects who are unwilling to practice safe sex (use male or female condom) for the duration of the study.

36. [REDACTED]
- [REDACTED]
 - [REDACTED]
 - [REDACTED]

37. Significant risk for suicidal behavior, in the opinion of the Investigator.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This study will be a non-randomized, single-center, open-label, parallel group, 2-treatment study. Each subject will receive 1 treatment, depending on the cohort in which they participate.

Subjects who have met all eligibility criteria will receive a subject number upon inclusion in the study (subject numbers: 01 - 16; 01 to 08 for Group 1 and 09 to 16 for Group 2). 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 (e.g., 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 (unlabeled; for oral administration) and [¹³C]-labeled balovaptan (for IV infusion).

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Balovaptan

RO5285119/F17 10 mg dispersible film-coated tablets will be supplied by the Sponsor in high-density polyethylene bottles. For information on the formulation and handling of balovaptan, see the Investigational Medicinal Product Dossier.

4.3.1.2 [¹³C]-Labeled Balovaptan

The [¹³C]-labeled balovaptan drug substance will be supplied by the Sponsor. RO5285119/F40 [¹³C]-labeled balovaptan solution (20 µg/ml) for IV infusion will be prepared by the site. For information on the formulation and handling of [¹³C]-labeled balovaptan, see the Investigational Medicinal Product Dossier.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any overdose or incorrect administration of any of the study treatments 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 eCRF.

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

4.3.2.1 Balovaptan (Oral Administration)

An oral dose of balovaptan 10 mg (Cohort 1) or 50 mg (Cohort 2) will be administered in the morning of Day 1 of Period 1 and each morning of Days 1 to 14 of Period 2. On Days 1 of Period 1 and Days 7 and 14 of Period 2, study drug administration will be after an overnight fast of at least 10 hours, followed by another 4 hours of fasting until lunch. On the other dosing days, study drug administration will take place at least 30 minutes before breakfast. Water will be allowed ad libitum until 1 hour prior to dosing and from 1 hour post dosing, and a maximum of 3 liters a day.

Study drug will be swallowed whole with 240 mL of still water.

4.3.2.2 [¹³C]-Labeled Balovaptan

On Day 1 of Period 1 and on Day 14 of Period 2, a single microdose of [¹³C]-labeled balovaptan 0.1 mg will be administered by a 15-minute constant IV infusion. The IV infusion will start 1.25 hours after administration of the oral dose of unlabeled balovaptan on Day 1 of Period 1 and Day 14 of Period 2.

Details on study drug preparation by the PRA Health Sciences (PRA) pharmacy will be described in the Manufacturing Batch Record, which will be prepared by the PRA pharmacy.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (balovaptan tablets and the [¹³C]-labeled balovaptan drug substance for IV infusion) 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.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) 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 Accountability Form and Drug Dispensing Form.

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., 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

Existing hormonal contraceptives and hormone replacement therapy regimens must remain unchanged during the conduct of the study. However, women of childbearing potential must agree to combine hormonal contraceptive methods with a barrier method for 90 days after the last dose of study drug. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.

Acetaminophen/paracetamol is allowed up to a maximum dose of 2 g/day up to 48 hours prior to dosing and during the in-house portion of the study, but total should not exceed 4 g total during the week prior to dosing. Subjects will be instructed not to exceed these limits.

4.4.2 Prohibited Therapy

Any prescribed systemic or topical medication within 4 weeks (or within 5 times the elimination half-life of the medication, whichever is longer) prior to the first study drug administration through the follow-up visit, or any slow release medicinal formulations considered to still be active within 4 weeks (or within 5 times the elimination half-life of

the medication, whichever is longer) prior to the first study drug administration are prohibited through the follow-up visit, 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 or herbal remedies are prohibited for 7 days prior to the first study drug administration through follow-up.

This is with the exception of medications to treat AEs, unless the rationale for the exception is discussed and clearly documented between the Investigator, the medical and safety monitor and the Roche clinical pharmacologist, and with the exception of permitted therapies per Section 4.4.1. 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 to as mentioned above:

- Any inhibitor of CYP3A taken within 4 weeks (or within 5 half-lives, whichever is longer) 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 (or within 5 half-lives, whichever is longer) 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 medical 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

Use of the following foods is prohibited as described below:

- Consumption of methylxanthine-containing products (e.g., coffee, tea, cola, chocolate) will be forbidden from 24 hours prior to balovaptan dosing and during the stays in the CRU.
- It is not permitted to take any nutrients known to modulate cytochrome CYP3A activity (e.g., grapefruit or grapefruit juice; Seville orange) within 2 weeks prior to first dosing until discharge from the CRU in Period 2.
- Subjects should refrain from consumption of any foods containing poppy seeds within 48 hours (2 days) prior to screening and each admission to the CRU to avoid false positive drug screen results.

4.4.4 Additional Restrictions/Considerations

- Subjects should have fasted for at least 4 hours prior to the screening visit, each admission to the CRU, and the follow-up visit.

- Water will be allowed ad libitum except for 1 hour before and 1 hour after oral dosing on Day 1 of Period 1 and Days 7 and 14 of Period 2. The excessive consumption of fluids (greater than 3 liters per day) should be avoided.
- On Day 1 of Period 1 and Days 7 and 14 of Period 2, oral balovaptan will be administered after an overnight fast of at least 10 hours. In addition, fasting will be continued until at least 4 hours post oral dose. On these days, standardized meals will be served to all subjects at the times noted in [Appendix 1](#). On these days a standardized lunch, afternoon snack, dinner, and evening snack will be served at similar times of the day, and subjects will be required to complete the meal.

On dosing days other than Day 1 of Period 1 and Days 7 and 14 of Period 2, oral balovaptan will be administered at least 30 minutes prior to breakfast. On these dosing days, meals will not be standardized.

During the remainder of the in-house periods, breakfast, lunch, dinner, and afternoon/evening snacks will be provided according to PRA standards.

- Between the screening visit and follow-up, alcohol must be restricted to no more than 2 units per day (1 unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits). Alcohol consumption will not be allowed 48 hours before balovaptan dosing and while staying in the CRU. Random alcohol/drugs of abuse testing may be employed throughout the study to verify compliance.
- Subjects should refrain from strenuous exercise for at least 96 hours prior to first dosing until 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 (ICFs) 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 recorded at baseline. In addition, all medications (e.g., 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 screening and at follow-up visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and 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 eCRF.

Height, weight and BMI will be determined at screening. Weight measurements will be repeated on the days indicated in [Appendix 1](#).

4.5.4 Vital Signs

Body temperature (tympanic), blood pressure, and pulse rate measurements will be collected on the days 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.

4.5.5 Laboratory, Pharmacokinetic, and Other Biological Samples

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

Biological samples will be destroyed when the final clinical study report (CSR) 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

Laboratory samples will be collected at the time points indicated in [Appendix 1](#). Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor subject safety.

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 and percent differential WBC count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).
- **Coagulation:** prothrombin time (International Normalized Ratio [INR]) and activated thromboplastin time (aPTT).
- **Blood chemistry panel:** sodium, potassium, chloride, bicarbonate, glucose (fasting), urea, creatinine, total protein, albumin, phosphate, calcium, total and conjugated bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), CPK, lactate dehydrogenase (LDH).
- **Urinalysis:** A midstream, clean-catch urine specimen will be collected for dipstick analysis of pH, glucose, leukocytes, nitrites, protein and blood. Microscopy will be performed if abnormalities are observed and if 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.
- **Drugs of abuse** (including cannabinoids, amphetamines [including ecstasy], methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates), alcohol and cotinine will be measured in urine at screening and each admission to the CRU (Day -1 and Day 14).
- **Viral serology:** HIV-1 and HIV-2 antibodies, HBsAg, HepBc-antibody and HCV antibody at screening only.
- **Pregnancy test:** follicle-stimulating hormone (FSH) and beta-human chorionic gonadotropin (serum pregnancy test) will be performed at screening in all females. At other time points, a serum pregnancy test will be performed in all females.

4.5.5.2 Pharmacokinetic Blood Samples

Pharmacokinetic samples will be taken via an indwelling catheter or by direct venipuncture at the time points in [Appendix 1](#) and [Appendix 2](#).

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

Plasma samples collected for PK analysis will be destroyed 6 months after the final CSR has been issued.

[REDACTED]

[REDACTED]

4.5.5.4 Clinical Genotyping Samples

A mandatory 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 CSR 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 ECGs will be collected at the time points indicated in [Appendix 1](#). Electrocardiograms will be collected after the subject has rested in a supine position for at least 5 minutes.

Time of the assessments will be recorded directly in the eCRF. The ECG will be judged by the Investigator and the judgment documented directly on the ECG printout, which will be kept as a source document and added to the study record. The following ECG parameters will be recorded: HR, PR-interval, QRS-duration, QT-interval, QTc-interval

(Fridericia's), T-wave and U-wave, and the interpretation of the ECG profile by the Investigator.

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 [REDACTED] concentrations of balovaptan and its metabolites M2 [REDACTED], and M3 [REDACTED] will be measured using separate specific and validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

Plasma concentrations of [¹³C]-labeled balovaptan will be measured using another 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
- [REDACTED]
- PK blood sampling
- Laboratory safety tests, clinical genotyping sample and urine collection
- Study drug administration
- Provide standard meal

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 CRU 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 CRU 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. Subjects who withdraw from the study may be replaced. The decision regarding the replacement of subjects will be documented.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. 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.

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5.1.2 Management of Toxicities and of Subjects Who Experience Adverse Events

5.1.2.1 Management Guidelines

In general, any emerging AEs 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 to treat the AE.

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

The Investigator should also consider discontinuation of treatment with balovaptan, in particular in case an AE is of severe intensity and considered to be possibly related to balovaptan.

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 PK objectives. Dose modifications because of an AE are not allowed in this study.

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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 GCP, 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 [5.3.5.9](#) for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., 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 (i.e., the AE actually causes or leads to death)
- Is life threatening (i.e., 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 [5.3.5.10](#))

- Results in persistent or significant disability/incapacity (i.e., 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 (e.g., 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 (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; 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 AEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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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 eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each AE recorded on the Adverse Event eCRF, 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 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 (e.g., 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 a serious adverse event (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 adverse event 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 adverse event and administration of the study drug, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO (NOT RELATED)	<u>An adverse event will be considered related, unless it fulfills the criteria specified below.</u> Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., 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 eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For AEs other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., 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 eCRF. 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.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., 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 eCRF. 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 eCRF if it is unclear as to whether the events are associated.

5.3.5.4 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 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 eCRF (and Form, if appropriate). If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF if already completed should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

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 eCRF (and Form if appropriate).

5.3.5.5 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 (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., 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 (e.g., alkaline phosphatase and bilirubin $5 \times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event 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 eCRF (and Form if appropriate), along with a descriptor indicating whether the test result is above or below the normal range (e.g., "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 eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

5.3.5.6 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 (e.g., 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 (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event 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 eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

5.3.5.7 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 eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a SAE or an AE of special interest (see Section 5.4.2).

5.3.5.8 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 eCRF 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. 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. If the cause of death later becomes available (e.g., 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 (e.g., "sudden cardiac death").

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

5.3.5.9 Preexisting Medical Conditions

A preexisting 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 preexisting 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, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., 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 preexisting 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:

- SAEs (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)

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., 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 (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information:

Medical Monitor: [REDACTED], M.D. (Primary)
Telephone No.: [REDACTED]
Mobile Telephone No.: [REDACTED]
Medical Monitor: [REDACTED], M.D. (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 (i.e., 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 AEs 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 (i.e., 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 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 (i.e., 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 (e.g., 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. 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 ICF 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 (i.e., 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 reported to the Sponsor immediately (i.e., 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 a SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., 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 eCRF (and Form if appropriate) and reported to the Sponsor immediately (i.e., 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 (e.g., 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.

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

- Accidental overdose: Enter the AE 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 2 Adverse Event eCRF pages (and Forms if appropriate), 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.

5.5 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 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, AEs 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 (e.g., 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 as 21 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment. 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 AEs 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) IB.

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 the absolute bioavailability of the 10 mg single dose with sufficient precision.

A total of 8 subjects per cohort are to be enrolled with the target of at least 6 subjects available for the primary PK analysis (i.e., having taken a single dose of 10 mg on Day 1 and completed all PK assessment up to Day 10). If the number of subjects providing PK data from the multiple dose parts of the study is lower than 6 for either cohort more subjects may be enrolled.

Assuming a within-subject variability of around 35% it can be estimated that with 6 subjects the half-width of the 90% confidence interval (CI) for the ratio of geometric means of the microdose IV kinetics with that from the oral dose (i.e. CL versus CL/F) would be obtained by dividing/multiplying the ratio estimate by a factor of 1.50.

The within-subject variability value of around 35% has been identified as a reasonable assumption: it is smaller than the observed 42% between-subject variability for the apparent clearance of distribution (CL/F) from a single oral 10 mg dose in study WP40038, and it considers that the reference will be obtained from IV kinetics, which is expected to be less variable than oral kinetics.

Table 4 Precision Factor Estimates

<i>Number of Subjects</i>	<i>Variability</i>	<i>Precision Factor</i>
6	30%	1.42
	35%	1.50
	40%	1.59

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 cohort.

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

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

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 time point for balovaptan, M2, and M3, and individual plasma [¹³C]-labeled balovaptan concentrations 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 semi-logarithmic scales.

The primary PK parameter is absolute bioavailability (F) for balovaptan following a single 10 mg dose.

The following plasma PK parameters will be estimated for balovaptan, M2, M3, and [¹³C]-labeled balovaptan:

- C_{max} : Maximum observed plasma concentration

- t_{\max} : Time to maximum observed plasma concentration
- $t_{1/2}$: Apparent terminal half-life
- AUC_{last} : Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration time point (following a single oral dose)
- AUC_{inf} : Area under the plasma concentration-time curve from time zero extrapolated to infinity (following a single dose)
- AUC_{0-24} : Area under the plasma concentration-time curve over the dosing interval at steady state
- C_{last} : Last measurable plasma concentration
- C_{trough} : Concentration measured at the end of the dosing interval
- t_{last} : Time of last measurable plasma concentration
- λ_z : Terminal elimination rate constant
- R_{AUC} : Accumulation ratio for AUC_{τ} (Day 14 $AUC_{0-\tau}$ / Day 1 $AUC_{0-\tau}$)
- $R_{C_{\max}}$: Accumulation ratio for C_{\max} (Day 14 C_{\max} / Day 1 C_{\max})
- $R_{C_{\text{trough}}}$: Accumulation ratio for C_{trough} (Day 14 C_{trough} / Day 1 C_{trough})

The following plasma PK parameters will be estimated for the parent compound balovaptan:

- F : Absolute bioavailability
- CL : Total body clearance (IV administration only)
- V_{ss} : Volume of distribution

█ plasma concentration ratios will be calculated for balovaptan, M2, and M3, as applicable.

Additional PK parameters may be derived if deemed necessary.

All PK parameters will be presented by individual listings and summary statistics by treatment including arithmetic means, geometric means, medians, ranges, standard deviations and coefficients of variation.

6.7 Genotyping ANALYSES

The relationship between CYP3A4 genotype and steady state balovaptan exposure will be evaluated. Other isoforms may also be analyzed.

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, will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (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 the PRA, using the 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 CRFs 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

The eCRF design will be performed with the computer program Oracle Clinical (Oracle, Redwood Shores, Redwood City, CA, USA) by the Database Programming Department of PRA.

All eCRFs should be completed by designated, trained site staff. eCRFs 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 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., 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, subject-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, subject 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 (i.e., 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 7.5.

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.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper subject-reported data (if applicable), ICFs, 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 GCP 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 US or under a US Investigational New Drug (IND) application will comply with US Food and Drug Administration (FDA) 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 ICF (and ancillary sample ICFs such as a Child's Informed Assent Form or Mobile Nursing ICF, 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 ICFs 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 ICF 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 ICFs, 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 ICF (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, ICFs, 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 GCP guidelines and require reporting to health authorities. As per the Sponsor's SOPs, 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 16 subjects.

Central facilities will be used for certain study assessments throughout the study (e.g., 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

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 CSR. 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.

The Investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

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 to the study conduct, except for changes necessary to eliminate an immediate hazard to subjects or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1 Schedule of Activities (cont.)

AE = adverse event; BMI = body mass index; CG = clinical genotyping; CRU = clinical research unit; [REDACTED]; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; FSH = follicle-stimulating hormone; IV = intravenous; PK = pharmacokinetic.

- a Subjects will be admitted to the CRU on Day -1 and will be allowed to leave when all assessments on Day 10 have been completed. Subjects will return in the afternoon of Day 14 of Period 1 (which is also Day -1 of Period 2) and will be allowed to leave when all assessments on Day 19 have been completed.
- b The IV infusion of the microdose will start 1.25 hours after the oral study drug administration on Day 1 of Period 1 and Day 14 of Period 2.
- c On Day 1 of Period 1, and Days 7 and 14 of Period 2, subjects are fasted for at least 10 hours prior to dosing. Water will be allowed ad libitum until 1 hour prior to dosing and from 1 hour after dosing. No food is allowed for at least 4 hours postdose. Standardized lunch and dinner are provided 4 and 10 hours postdose, respectively, on Day 1 of Period 1, and Days 7 and 14 of Period 2. Standardized afternoon and evening snacks will be provided as well on these days.
On the other dosing days in the multiple dosing period, subjects will be dosed at least 30 minutes prior to breakfast. On these dosing days, meals will not be standardized.
- d All PK sampling times are relative to oral dosing (see also [Appendix 2](#)).
[REDACTED]
- f Includes measurement of height and BMI.
- g Triplicate ECGs will be collected at screening and Day -1 of Period 1 only. At all other time points a single ECG will be collected (Period 1: Day 10; Period 2: Day -1 of Period 2; predose on Days 6 and 11; Day 18 (96 hours after last dosing); follow-up).
- h Vital signs will be measured at screening (in triplicate), and in Period 1: on Day -1 (in triplicate), Day 1 at 3 hours postdose, Day 2, Day 5; in Period 2: on Day -1, predose on Days 1, 7 and 14; on Day 18 (96 hours after last dosing); follow-up. At screening and on Day -1 of Period 1, vital signs will be measured in triplicate; at other time-points, vital signs will be single measurements.
- i For females only: FSH and serum pregnancy test at screening, and serum pregnancy test only at all other time points.
- j Hematology samples will be collected at screening, Day -1 of Period 1, Day -1 of Period 2; predose on Days 6 and 11 of Period 2; Day 18; follow-up.
- k Biochemistry samples will be collected at screening, Day -1 of Period 1, Day -1 of Period 2; predose on Day 11 of Period 2; Day 18; follow-up.
[REDACTED]

Appendix 2 Schedule of Pharmacokinetic Blood [REDACTED] Samples

Procedure		Blood sampling for balovaptan and M2, M3 metabolites							Blood sampling for ¹³ C-balovaptan		[REDACTED]	
		Period 1	Period 2							Period 1	Period 2	Period 2
Study Day		1	1	2	7	8	12	13	14	1	14	12
Predose		X	X	X	X	X	X	X	X			
Hours Post Oral Dose	0.25	X										
	0.5	X							X			
	1	X							X			
	1.25	X							X	X ^a	X ^a	
	1.33	X							X	X	X	
	1.5	X							X	X	X	
	1.75	X							X	X	X	
	2	X			X				X	X	X	
	2.25	X							X	X	X	
	2.5	X							X	X	X	
	3	X			X				X	X	X	X ^b
	3.5	X							X	X	X	
	4	X			X				X	X	X	
	4.5	X							X	X	X	
	5	X							X	X	X	
	6	X			X				X	X	X	
	8	X							X	X	X	
	12	X			X				X	X	X	
	16 (P1/D2 or P2/D15)	X (D2)				X			X (D15)	X	X (D15)	
	24 (P1/D2 or P2/D15)	X (D2)							X (D15)	X	X (D15)	
	48 (P1/D3 or P2/D16)	X (D3)							X (D16)	X	X (D16)	
60 (P1/D3 or P2/D16)	X (D3)							X (D16)	X	X (D16)		
72 (P1/D4 or P2/D17)	X (D4)							X (D17)	X	X (D17)		
96 (P1/D5 or P2/D18)	X (D5)							X (D18)	X	X (D18)		
108 (P1/D5 or P2/D18)	X (D5)							X (D18)	X	X (D18)		
120 (D6)	X (D6)											
144 (D7)	X (D7)											
168 (D8)	X (D8)											
192 (D9)	X (D9)											
216 (D10)	X (D10)											

Appendix 2

Schedule of Pharmacokinetic Blood and CSF Samples (cont.)

[REDACTED]; P1 = Period 1; P2 = Period 2.

^a Sample to be taken as shortly as possible prior to start of intravenous infusion.

[REDACTED]