Official Title: A Phase Ib, Multicenter, Open-Label, 6-Week Study With a 48-Week Extension to Investigate the Pharmacokinetics, Safety, and Tolerability of Balovaptan in Children Ages 2–4 Years With Autism Spectrum Disorder

NCT Number: NCT04049578

Document Date: Protocol Version 2: 08-July-2019

PROTOCOL

TITLE:	**A PHASE Ib, MULTICENTER, OPEN-LABEL, 6-WEEK STUDY WITH A 48-WEEK EXTENSION TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF BALOVAPTAN IN CHILDREN AGES 2–4 YEARS WITH AUTISM SPECTRUM DISORDER**
PROTOCOL NUMBER:	WP40877
VERSION NUMBER:	2
EUDRACT NUMBER:	2019-000989-38
IND NUMBER:	116483
TEST PRODUCT:	Balovaptan (RO5285119)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	23 March 2019
DATE AMENDED:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
08-Jul-2019 13:15:06	[redacted]	[redacted]

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol WP40877 has been amended primarily in response to requests received from the [redacted]. Changes to the protocol are summarized below:

- Blood pressure parameters at screening that will result in exclusion from the study have been added (Section 4.1.2.2 and [redacted]).
- Heart rate parameters at screening that will result in exclusion from the study have been added (Section 4.1.2.2).
- Text has been added to clarify study treatment administration, including the definitions of fasted and fed states (Section 4.3.2).
- Head circumference will be only measured up to 3 years of age given the availability of Centers for Disease Control and Prevention published nomograms (Section 4.5.3, [redacted]).
- [redacted]
- ECG assessments have been revised to include chest leads in addition to limb leads to ensure consistent ECG machine based reading algorithm (Section 4.5.8, [redacted]).
- The length of time subjects must be supine prior to ECG assessment has been changed to 5 minutes (if possible) (Section 4.5.8, [redacted]).
- Subjects who experience failure to thrive, worsening nutritional status, or significant food refusal in the opinion of the investigator must discontinue study treatment (Section 4.6.1.).
- [redacted]
- [redacted]
- The tertiary Medical Monitor has changed (Section 5.4.1).
- The window for the Week 2 visit has been changed from ±2 days to +4 days to ensure all subjects are at steady state. The Week 6 visit window has been changed from ±2 days to ±4 days to give sites and patients more flexibility for scheduling this study visit [redacted].
- Serum chemistry samples will be obtained from all subjects at Week 6 [redacted].

- The option to not repeat the Autism Diagnostic Observation Schedule™, Second Edition (ADOS-2) assessment at screening if an ADOS assessment had been performed by a certified rater and was documented within 12 months of the screening visit was modified to ensure diagnostic specificity for very young children (Section 4.1.1).
- [redacted]

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib, MULTICENTER, OPEN-LABEL, 6-WEEK STUDY WITH A 48-WEEK EXTENSION TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF BALOVAPTAN IN CHILDREN AGES 2–4 YEARS WITH AUTISM SPECTRUM DISORDER**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib, MULTICENTER, OPEN-LABEL, 6-WEEK STUDY WITH A 48-WEEK EXTENSION TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF BALOVAPTAN IN CHILDREN AGES 2–4 YEARS WITH AUTISM SPECTRUM DISORDER**
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Objectives and Endpoints

This study will evaluate the pharmacokinetics, safety, and tolerability of 4 mg balovaptan once a day (QD) (the predicted 10-mg adult equivalent dose) administered for 6 weeks to children 2–4 years old with autism spectrum disorder (ASD). The study will also provide a preliminary evaluation of efficacy of treatment with 4 mg of balovaptan QD in this age group.

Pharmacokinetic Objectives

The primary pharmacokinetic (PK) objective for this study is to investigate the plasma exposure at steady-state (area under the concentration–time curve at steady state [AUC_{ss}]) of balovaptan in subjects ages 2–4 years old and to determine the dose that will deliver adult-equivalent exposure in subjects ages 2–4 years. The primary PK objectives will be based on the following endpoint:

- Balovaptan AUC_{ss} estimates, as derived using a population-pharmacokinetic (pop-PK) modeling approach

The secondary PK objective for this study is to investigate the pharmacokinetics of balovaptan and its metabolites M2 (as applicable) and M3 in subjects aged 2–4 on the basis of the following endpoints:

- Plasma concentration of balovaptan and its metabolites M2 (as applicable) and M3 at specified timepoints
- Plasma concentration ratio of M2 (as applicable) to balovaptan and M3 to balovaptan
- Other PK parameters as appropriate

Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of treatment with 10-mg equivalent dose balovaptan on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale
- Incidence and severity of treatment-emergent abnormalities in physical and neurologic examinations

- Change from baseline in vital signs
- Change from baseline in ECG parameters
- Change from baseline in clinical laboratory test results
- [redacted]

Exploratory Efficacy Objective

The exploratory objective of this study is to make a preliminary evaluation of the clinical activity of balovaptan on the basis of the following endpoints:

- Change from baseline on the Vineland™ Adaptive Behavior Scales, Second Edition (Vineland-II) two-domain composite (2DC) score (defined as the mean of the Communication domain standard score and the Socialization domain standard score) at Weeks 6, 12, 24, and 54
- Change from baseline on severity of clinical impressions as measured using the Clinical Global Impressions-Severity (CGI-S) at Weeks 6, 12, 24, and 54
- Change from baseline on clinical impressions as measured using the Clinical Global Impressions-Improvement (CGI-I) at Weeks 6, 12, 24, and 54
- Change from baseline on severity of clinical impressions as measured using the Caregiver-Reported Global Impression of Change (CaGI-C) and Caregiver-Reported Global Impression of Severity (CaGI-S) at Weeks 6, 12, 24, and 54

Additional Objective

An additional exploratory objective for this study is to evaluate the palatability of balovaptan in subjects 2–4 years old on the basis of the following endpoint:

- Palatability test of study drug given after administration of balovaptan at Week 6

Study Design

Description of Study

This is a Phase Ib, multicenter, open-label study in children 2–4 years old with ASD to investigate the pharmacokinetics, safety, and tolerability of oral doses of 4 mg balovaptan QD, which is predicted to *be adult-equivalent, i.e., provide a plasma exposure range that is comparable to that following* oral doses of 10 mg balovaptan QD *in adults*. The study consists of a 6-week treatment period to evaluate the pharmacokinetics of balovaptan in 2- to 4-year old children followed by an optional extension period of 48 weeks.

Subjects for whom consent has been provided by their parent or legal guardian will undergo screening within 4 weeks prior to the first study drug administration. Eligible subjects will be enrolled in an open-label fashion and treated with 4 mg balovaptan.

The safety of balovaptan will be assessed by monitoring of adverse events, serious adverse events, clinical laboratory values, ECGs, physical and neurologic examinations, and safety outcome assessments such as suicidality. Exploratory efficacy endpoints will examine core autism symptoms (social interaction, social communication) and functional deficits.

The total duration of the study (from screening through to study completion) for each subject will be approximately 12 weeks or 60 weeks, depending on whether or not he or she participates in the optional extension period, divided as follows:

- Screening period: approximately 4 weeks
- Treatment period: 6 weeks
- Optional extension period: 48 weeks
- Post-treatment follow-up period: 2 weeks

Screening Period

Subjects whose parent or legal guardian has given their consent for the subject to participate in the study will undergo a screening procedure within 4 weeks before the first study drug

administration (Day 1). Subjects must meet all of the eligibility criteria in order to qualify for the study.

In cases in which the screening laboratory samples are rejected by the central laboratory (e.g., a hemolyzed sample) or if the results are not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated within the screening period. If retesting is not possible within the 4-week screening window, the screening period may be prolonged but should not exceed 6 weeks. It should also be verified that the subject continues to meet all other eligibility criteria.

Specific samples for laboratory tests and assessments at baseline do not need to be repeated if the baseline visit occurs within 2 weeks after the screening visit and no clinically relevant abnormal results have been identified at screening and no clinical abnormalities have emerged since screening that require mandated laboratory assessments in the opinion of the investigator.

Six-Week Treatment Period

All subjects will receive 6 weeks of treatment with an oral dose of 4 mg of balovaptan QD, which is predicted to be equivalent to the adult oral dose of 10 mg balovaptan QD. Study enrollment will occur only after a subject has met all eligibility criteria. At the baseline visit (Day 1), subjects will undergo a series of assessments outlined in the schedule of activities.

The target exposure range for a 10-mg equivalent dose is based on the observed exposure distribution in adults receiving 10 mg balovaptan QD in Study BP28420, with a median AUC during the dosing interval tau at steady state ($AUC_{\tau,ss}$) of approximately 1000 ng•hr/mL, interquartile range of approximately 700–1400 ng•hr/mL, and 90% of $AUC_{\tau,ss}$ values (5th–95th percentile) within approximately 400–2000 ng•hr/mL.

For the first subject, if the $AUC_{\tau,ss}$ is $>$ 2000ng•hr/mL or $<$ 400 ng•hr/mL, then the dose will be adjusted with the aim to get $AUC_{\tau,ss}$ as close as possible to the target 1000 ng•hr/mL. Any new subject to be enrolled will receive this adjusted dose, unless cumulative data from all subjects in the study indicate that further dose adjustments are required to be within the target distribution. If required based on accumulating PK data, the dose may be adjusted further. It is planned that any dose change will be implemented for all enrolled subjects and any additional enrolled subjects. However, if indicated based on large variability in the systemic exposure of balovaptan, different doses may potentially be given for children of different ages or adjustment of dose may potentially be done for a given individual subject so that plasma exposures are not outside the targeted range for an extended period of time. Subjects should come to the site for an unscheduled study visit as soon as possible after a dose change is confirmed if subjects cannot receive the new study drug supply at the next regular study visit early enough or if any other relevant clinical, administrative, or operational reasons call for an additional study visit. The decision to change the dose will be made by the Sponsor and communicated to sites.

If treatment interruption occurs between Day 1 and Week 2 (the PK sampling visit), after consultation with the clinical pharmacologist, subjects may need to be withdrawn and replaced or the Week 2 PK visit may be delayed.

Optional Extension Period

All subjects who complete the 6-week treatment period, and in the view of the investigator, have not experienced relevant adverse events considered prohibitive for further treatment are eligible for participation in the extension period of the study. The transition into the extension period is seamless; subjects will continue to receive study drug treatment without interruption after the end of the 6-week period. Subjects who do not participate in the extension period of the study will complete the follow-up visit 2 weeks after their final dose.

The 48-week duration of the extension period serves to evaluate the long-term safety, tolerability, and exploratory efficacy of balovaptan treatment in young children with ASD. All subjects will continue to receive an oral dose of 4 mg balovaptan QD, which is predicted to be equivalent to the adult oral dose of 10 mg balovaptan QD. If a change in dose occurs, all

subjects in the 6-week treatment period and all subjects in the extension period will receive the new dose at the earliest opportunity.

Follow-Up Period

In the case of treatment discontinuation during the 6-week treatment period or extension period, in order to continue to assess the safety and tolerability of balovaptan, subjects should return to the site 2 weeks after their final dose. Subjects who complete the 6-week treatment period but who do not enter the extension period and subjects who complete the extension period should also return to the site 2 weeks after their final dose for a follow-up visit.

Number of Subjects

Approximately 10 subjects will be enrolled at approximately 10 international sites, including sites in North America and Spain.

Target Population

Inclusion Criteria

Subjects must meet the following criteria for study entry:

- Parent or legal guardian/representative willing and able to give written informed consent according to local requirements and subject willing and able to provide informed assent or consent according to local requirements
- Males or females 2–4 years of age at the time of signing Informed Consent Form
- Diagnosis of ASD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for ASD

  Diagnostics will be performed by a team of autism experts and confirmed by Autism Diagnostic Observation Schedule™, Second Edition (ADOS-2) criteria. The DSM-5 criteria for diagnosis of autism must be met with the highest confidence in the opinion of the investigator. Children with ambiguous diagnostic results cannot be enrolled in the study.

  If the ADOS-2 assessment has been performed by a certified rater and documented within 12 months of the screening visit, *it is not mandatory to repeat it unless the subject was assessed below an age of 2 years.*
- Hearing and vision compatible with the study assessments, as judged by the investigator
- Ability for subject and the caregiver to comply with the study protocol, in the investigator's judgment
- Availability of a parent or other reliable caregiver who is fluent in language of the site and has frequent and sufficient contact with the subject

  The same person should accompany and agree to provide information about the subject's behavior and symptoms at the baseline and Week 6, 12, 24, and 54 visits.

Exclusion Criteria

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

- Clinically significant psychiatric and/or neurologic comorbidity that may interfere with the safety or efficacy endpoints in the view of the investigator
- Clinically significant regression of any acquired language and motor function skills in the opinion of the investigator throughout the subject's development
- History of seizures with the exception of a single, non-complicated febrile seizure $\geq$6 months before screening
- Clinical diagnosis of peripheral neuropathy or signs and symptoms indicative of peripheral neuropathy
- Any clinically relevant cardiovascular disease
- Confirmed elevation in cardiac troponin I (cTn I), high-sensitive cardiac troponin T (hs cTn T), N-terminal pro–B-type natriuretic peptide (NT-proBNP) or, if conducted, clinically relevant abnormality in Doppler echocardiogram

- Confirmed (e.g., on two consecutive measurements) clinically significant abnormality on ECG at screening, including, but not limited to, a QT interval corrected through use of Fridericia's formula (QTcF) of ≥ 450 ms, absence of dominating sinus rhythm, or second- or third-degree atrioventricular block
- *Confirmed (e.g., on two consecutive measurements) systolic or diastolic blood pressure above the 95th percentile or below the 5th percentile according to the Centers for Disease Control and Prevention (CDC) norm tables referring to stature (height)-for-age percentiles.*
- *Confirmed (e.g., on two consecutive measurements) heart rate:*
  > 150 bpm in 2-year old children,
  > 135 bpm in 3-year old children, or
  > 120 bpm in 4-year old children.
- Concomitant disease or condition (pulmonary, gastrointestinal [GI], hepatic, renal, metabolic, immunological system) that could interfere with, or treatment of which might interfere with, the conduct of the study; or discontinuation of prohibited medication that might pose unacceptable risks to the subject in the opinion of the investigator
- Evidence for current GI disease that would interfere with the conduct of the study or pose unacceptable risks in the opinion of the investigator (e.g., GI bleeding, active stomach ulcer)
- History of coagulopathies, bleeding disorders, or blood dyscrasias
- Positive serology for HIV-1 or HIV-2
- Confirmed clinically significant abnormality in parameters of hematology, clinical chemistry, coagulation, or urinalysis, specifically a confirmed absolute neutrophil count (ANC) < LLN

  Children with confirmed CPK elevations exceeding 2 × upper limit of normal (ULN) will be excluded
- History of malignancy
- Participation in an investigational drug study within 90 days (or 5 times the half-life of the investigational molecule, whichever is longer) prior to treatment assignment, or participation in a study testing an investigational medical device within 90 days prior to treatment assignment or if the device is still active
- Presence of any clinically significant abnormality likely to interfere with the conduct of the study according to the judgment of the investigator
- Clinically significant loss of blood within 3 months prior to screening
- Unstable use of permitted medications for 4 weeks before screening
- Use of prohibited medications within 30 days (or 5 times the half-life, whichever is longer) prior to initiation of study treatment
- Other severe medical comorbidity that may interfere with the safety or efficacy endpoints

End of Study

The end of study is defined as the date when the last subject, last visit occurs in the follow-up period. The end of the study is expected to occur 14 months after the last subject is enrolled.

Length of Study

It is anticipated that it may take up to 18 months to recruit all subjects for the study. Hence, the total length of the study from screening of the first subject to the end of the study is estimated to be approximately 2.5–3 years.

Investigational Medicinal Product

The investigational medicinal product (IMP) for this study is balovaptan.

Test Product (Investigational Drug)

Balovaptan will be supplied by the Sponsor as dispersible tablets at a dose strength of 4 mg QD, which is predicted to be equivalent to the adult oral dose of 10 mg balovaptan QD. If a dose change during the study conduct occurs, dispersible tablets of dose strengths of 0.5 and 2 mg

may be used to achieve the median target AUC for a 10-mg adult dose equivalent. The tablets will be packaged within high-density polyethylene bottles.

Statistical Methods

Primary Analysis

Individual and mean plasma concentration data per timepoint will be listed for the parent and metabolite and the ratio of metabolite to parent concentration will be derived.

Nonlinear mixed-effects modeling will be used to analyze the sparse sampling dose-concentration-time data collected for balovaptan. A previously developed pop-PK model will be used to analyze the PK data in this study. Population and individual PK parameters will be estimated and $AUC_{\tau,ss}$ derived from the individual PK model parameter estimates. The dose resulting in an adult-equivalent exposure will be calculated from the ratio of apparent clearance (CL) estimates in 2- to 4- year-old children to apparent CL in adults.

The results of the pop-PK model based analyses may be reported in a document separate from the clinical study report.

Exposure equivalence with adult exposures after QD dosing with age-adjusted 10-mg dose of balovaptan will be confirmed, and if needed, dose-adjustment recommendations will be made for subjects continuing in the extension period.

Determination of Sample Size

The sample size required to determine the dose that will deliver adult-equivalent exposures in pediatric subjects was previously assessed for Study BP30153, based on a bootstrapping methodology combined with physiologically based PK (PBPK) exposure simulations. With a sample size of 10 children, the 90% CI for the apparent CL estimate was 74%–130% of the true apparent CL for the age group of 5- to 7 year old children, indicating that the derived adult-equivalent dose would result in exposures within approximately 30%–40% of the target exposure.

As the variability in apparent CL is expected to be similar in 2- to 4-year old children as in 5- to 17-year olds, the same sample size was assumed appropriate.

The primary CL mechanism of balovaptan is metabolism via cytochrome P450 3A4 (CYP3A4) (producing M1, M2, and M3) and to a minor extent by means of cytochrome P450 2D6 (CYP2D6) (producing M4). In humans, these systems are known to attain adult capacity per gram of liver tissue in the first few years of life as shown by in vitro enzyme expression data as well as based on clinical pharmacokinetics for known substrates. In children aged 8–17 years, it has been confirmed that no dose adjustment is required in order to achieve similar exposures as in adults, whereas in children ages 5–7 years, a reduction in CL of approximately 35% was detected. Approximately 10 subjects treated with active drug in the various age groups in Study BP30153 (8–11 years, 12–14 years, and 15–17 years) have shown to be sufficient to determine the dose that provides equivalent exposure as observed in adults treated with 10 mg with adequate precision.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2DC	two-domain composite (score)
ADOS-2	Autism Diagnostic Observation Schedule™, Second Edition
ANC	absolute neutrophil count
ASD	autism spectrum disorder
AUC	area under the concentration–time curve
$AUC_{\tau,ss}$	area under the concentration–time curve during the dosing interval tau at steady state
AVP	arginine vasopressin
AVPR1A	arginine vasopressin receptor 1A
BMI	body mass index
CaGI-C	Caregiver-Reported Global Impression of Change
CaGI-S	Caregiver-Reported Global Impression of Severity
CDC	Centers for Disease Control and Prevention
CGI-I	Clinical Global Impressions of Improvement
CGI-S	Clinical Global Impressions of Severity
CL	clearance
ClinRO	clinician-reported outcome
C-SSRS	Columbia-Suicide Severity Rating Scale
cTn I	cardiac troponin I
CYP2D6	cytochrome P450 2D6
CYP3A4	cytochrome P450 3A4
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	Ethics Committee
eCOA	electronic clinical outcome assessment
eCRF	electronic Case Report Form
EDC	electronic data capture
EU	European Union
FDA	Food and Drug Administration
GI	gastrointestinal
GLP	Good Laboratory Practice
HbA_{1c}	glycated hemoglobin
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
hs cTn T	high-sensitive cardiac troponin T

Abbreviation	Definition
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
NOAEL	no-observed-adverse-effect level
NT-proBNP	N-terminal pro B–type natriuretic peptide
ObsRO	observer-reported outcome
PBPK	physiologically based pharmacokinetic
PedsQL	Pediatric Quality of Life
P-gp	P-glycoprotein
PK	pharmacokinetic
Pop-PK	population pharmacokinetic (model)
QD	once a day
QRS	QRS interval on an ECG
QT	QT interval on ECG
QTc	corrected QT interval
QTcF	QT interval on ECG with Fridericia correction
SOC	Scientific Oversight Committee
SRS-2	Social Responsiveness Scale, Second Edition
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
Vineland™-II	Vineland™-II Adaptive Behavior Scales, Second Edition
V1a	vasopressin receptor type 1a
V1b	vasopressin receptor type 1b
V2	vasopressin receptor 2
VPA	valproic acid

1. BACKGROUND

1.1 BACKGROUND ON AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction and by restricted, repetitive patterns of behaviors, interests, or activities. The prevalence of ASD is between 1 in 50 and 1 in 88 children (Levy et al. 2009; CDC 2012) and approximately 1 in 42 boys and 1 in 189 girls (CDC 2016). Core symptoms of ASD are expected to emerge early in development, and are usually observed by 3 years of age, although higher-functioning children with more typical language development can have delayed identification of symptoms and diagnosis. It is estimated that approximately 1.2% of the overall population in the United States lives with ASD (Buescher et al. 2014), and it has been reported to be similar in the population in the United Kingdom (Brugha et al. 2011). The diagnosis rates in the United Kingdom for children with ASD are currently estimated to be 1.1% of the total population, thus suggesting that the prevalence rates between adults and children do not differ markedly. ASD is a persistent disorder diagnosed in children that carries a life-long burden from childhood throughout adulthood. Diagnosis rates in central and southern European countries such as Italy, Germany, Denmark, France, Spain and Poland are increasing but currently are much lower, with estimates around 0.1–0.6% (Aguilera et al. 2007; Bachmann et al. 2016; Ferrante et al. 2015; Fortea et al. 2013; Hansen et al. 2015; Skonieczna-Żydecka et al. 2017; Van Bakel et al. 2015).

Although parental developmental concerns and initial symptoms may be identified as early as 12–24 months of age, typically an ASD diagnosis is often delayed until early preschool age (Lodi et al. 2006). In the United States, the average age of diagnosis with ASD is approximately 4 years. However, increasingly in research and highly trained clinical settings, formal ASD diagnoses are being assigned as early as 18–24 months of age and overall show stability on follow-up (Chawarska et al. 2007; Kleinman et al. 2008). Nevertheless, diagnostic caution is exercised due to the recognition of marked changes in severity of symptoms in early life (Chawarska et al. 2009). Core deficits detectable early include impaired social communication, which manifests as impaired use of non-verbal communication; delayed and reduced interactions with caregivers; absent sharing of enjoyable experiences and interest; and lack of social judgment. Abnormalities in communication may include a delay in verbal language development, impaired expressive language, deficient language pragmatics, as well as stereotyped, repetitive, or idiosyncratic use of language. Females with early detectable impairments in social and communication function are typically more intellectually impaired (Fombonne et al. 2011; Stacy et al. 2014). Stereotyped and repetitive behavior manifests as a preoccupation with stereotyped or restricted interests, adherence to routines, rigidity, perseverative, motor mannerisms, preoccupation or fascination with parts of items, limited symbolic play, and unusual visual exploration.

In addition to these core deficits, individuals with ASD can suffer from a range of comorbid conditions, including irritability, depression or anxiety, attention deficits and disruptive behaviors, obsessive-compulsive symptoms, seizures, and sleep disruption.

The etiology of ASD is highly genetic, although environmental factors also contribute to risk. Heritability estimates from family and twin studies suggest that up to 90% of variance can be attributed to genetic factors (Levy et al. 2009).

At present, no pharmacological treatment exists for the core deficits of ASD and available treatments address only associated behavioral problems (Wink et al. 2010), despite research on multiple compounds. Non-pharmacological treatments have been developed to address the core symptoms; however, efficacy has not been proven in large clinical trials (Warren et al. 2011).

The hypothalamic neuropeptides vasopressin (also known as antidiuretic hormone) and oxytocin, in addition to their well-defined roles in the control of osmotic balance and in reproduction, appear to have prominent roles in the regulation of higher brain functions, such as learning and memory, emotional control, and social behaviors. Vasopressin mediates its effect via vasopressin receptors (vasopressin 1a [V1a], vasopressin 1b [V1b], and vasopressin 2 [V2]), which are all members of the G protein–coupled receptor family. V1a and V1b lead to intracellular increases in calcium through the phosphatidyl-inositol pathway, whereas V2 is coupled to adenylyl-cyclase and cyclic adenosine monophosphate production. V1a receptors are the primary subtype found in the CNS, expressed in several areas of the limbic system (hypothalamus, septum, hippocampus, and amygdala) but are also present in several tissues (vascular smooth muscle, liver, kidney, platelets, and spleen) (Loup et al. 1991; Ostrowski et al. 1994; Ostrowski 1998). V1b receptors are also present in several brain regions but appear to be the most important for the increase in corticotropin-releasing hormone–induced adrenocorticotropic hormone secretion. V2 receptors are present in the renal collecting duct and mediate the antidiuretic effects of vasopressin.

Studies in animals and humans have implicated the vasopressin system in the modulation of behaviors related to both core and associated symptoms of ASD. In non-human mammals, V1a receptors are distributed in brain regions associated with control of stress and anxiety and social and affiliative behaviors, including parental care, pair-bonding, social memory, and social aggression. Vasopressin levels have been shown to be elevated during stress, as induced by the forced swim test in rats (Ebner et al. 2002). Central administration of a V1 peptide antagonist has shown anxiolytic effects in an elevated plus-maze test, a standard animal model of anxiety (Liebsch et al. 1996), and antidepressant-like effects in the forced swim test, a model of depressive behavior. Similarly, V1a receptor knockout mice also show reduced anxiety in open-field, light-dark box, and elevated plus-maze tests (Bielsky et al. 2004; Egashira et al. 2007). In addition, central injection of arginine vasopressin (AVP) in rodents (voles and hamsters) has been shown to induce offensive aggressive behavior (Winslow et al.

1993; Delville et al. 1996), which can be prevented by a V1a receptor antagonist (Ferris et al. 2006). Scratching and excessive grooming, reminiscent of obsessive-compulsive behavior, can also be observed in mice after central injection of vasopressin (Meisenberg 1988).

In humans, support for a role of the vasopressin system in ASD is provided by studies on the arginine vasopressin receptor 1A (*AVPR1A*) gene that encodes the V1a receptor and is located on chromosome 12q. Multiple studies have shown genetic associations of the *AVPR1A* gene with ASD, mainly with genetic markers in the promoter region of the gene, which includes microsatellites. However, it is unclear which microsatellite alleles show association with ASD or specific clinical phenotypes (Kantojärvi et al. 2015). Consistent with behavioral studies in animals (see above), these risk alleles have been found to modulate activation of the amygdala during emotional face processing (Meyer-Lindenberg et al. 2009) and to be associated with specific personality traits in healthy volunteers (Ebstein et al. 2012). Similarly, intranasal administration of vasopressin was shown to modulate the activity of a network involved in the processing of emotional information with specific effects in the subgenual cingulate regions (Zink et al. 2010).

Additional evidence for a role of vasopressin in modulating behaviors of relevance to ASD is provided by studies showing increased cerebrospinal fluid concentrations of vasopressin in obsessive-compulsive disorder and aggressive behavior (Zink et al. 2010). Also, increased levels of AVP in plasma of subjects with ASD have been reported (Boso et al. 2007), although other researchers have been unable to replicate this observation.

In summary, there is a high unmet medical need for pharmacological treatments of these core symptoms of the disorder across the lifespan for individuals with ASD.

1.2 BACKGROUND ON BALOVAPTAN

Balovaptan is a potent and highly selective human V1a receptor antagonist that blocks the activation of the V1a G protein–coupled receptor.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.2.2 Clinical Studies

To date, balovaptan has been administered to 240 healthy subjects in eight Phase I studies (BP25694, BP28318, BP28977, BP29279, BP29412, WP40038, WP40608, and WP40609). Studies WP40608 and WP40609 have been completed, and preliminary data, including safety readouts, are available. Two other Phase I studies are ongoing: Study WP40607, an absolute bioavailability study, started in January 2019; [redacted] The highest multiple dose of balovaptan administered was 52 mg once a day (QD) in Study BP25694 (administered for 2 weeks) and in the functional magnetic resonance imaging proof-of-mechanism study BP29412 (administered for 6 days). Furthermore, doses of 50 mg QD given for 2 weeks are scheduled in Study WP40607 and Study WP40734.

In addition, balovaptan is in clinical trials in subjects with ASD. Study BP28420 (VANILLA) was a Phase II, proof-of-concept, randomized, double-blind, parallel-group study that evaluated the efficacy and safety of 1.5, 4, and 10 mg/day of balovaptan compared with placebo in male adults (aged 18–45 years) with ASD over a 12-week period. [redacted]

Study BP30153 (aV1ation) is an ongoing Phase II, multicenter, randomized, double-blind, 24-week, parallel-group, placebo-controlled, study in 5- to 17-year-old subjects assessing efficacy and safety of treatment with age-adjusted doses as high as the 10 mg/day adult equivalent dose of balovaptan. The study was initiated in November 2016.

[redacted]

1.2.2.1 Safety and Tolerability

[redacted]

In adult subjects with ASD in Study BP28420, balovaptan appeared to be safe and well tolerated. No treatment-emergent safety concerns were identified. In particular, no safety signals indicative of balovaptan-associated hematotoxicity, muscle toxicity, or neurotoxicity, reported in toxicology studies in animals, were observed. A total of eight serious adverse events in 4 subjects were reported in Study BP28420. The serious adverse events included suicidal ideation (placebo arm), sinus node dysfunction (1.5-mg arm), and syncope (4-mg arm). The syncopal serious adverse event occurred approximately 2 weeks after the final dose of balovaptan with an additional event of syncope reported approximately 6 weeks after the final dose. Approximately 16 weeks after the final dose the subject died as the result of suspected heart failure. [redacted]

No safety signals related to balovaptan have been identified in the ongoing Study BP30153 or in Study WN39434. [redacted]

[redacted]

1.2.2.3 Pharmacokinetics

In a single ascending dose study, exposure to balovaptan increased in a greater than dose-proportional manner following doses of 0.5–76 mg, whereas an approximately linear increase in exposure was observed after repeated dosing with 5–52 mg/day in healthy subjects. Balovaptan was rapidly absorbed with a median time to maximum concentration of 1 hour while subjects were in a fasted state and 3–4 hours after administration with food. Food had no relevant effect on the area under the concentration–time curve (AUC) of balovaptan. Steady state of balovaptan was achieved after approximately 7 days of daily dosing.

Renal excretion is the major pathway of elimination (approximately 53% of the drug material recovered), with most of the drug-related material in urine being composed of metabolites. An additional 30% of the administered dose was recovered in feces.

In the human mass balance study, two metabolites (M2 and M3) were qualified as major metabolites. Metabolites M2 and M3 are present in both toxicology species.

[redacted]

[redacted]

[redacted]

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, safety, and tolerability of 4 mg balovaptan QD (the predicted 10-mg adult equivalent dose) administered for 6 weeks to children 2–4 years old with ASD. The study will also provide a preliminary evaluation of efficacy of treatment with 4 mg of balovaptan QD in this age group.

2.1 PHARMACOKINETIC OBJECTIVES

The primary PK objective for this study is to investigate the plasma exposure at steady-state (AUC at steady state [AUC_{ss}]) of balovaptan in subjects ages 2–4 years old and to determine the dose that will deliver adult-equivalent exposure in subjects ages 2–4 years. The primary PK objective will be based on the following endpoint:

- Balovaptan AUC_{ss} estimates, as derived using a population-pharmacokinetic (pop-PK) modeling approach

The secondary PK objective for this study is to investigate the pharmacokinetics of balovaptan and its metabolites M2 (as applicable) and M3 in subjects aged 2–4 on the basis of the following endpoints:

- Plasma concentration of balovaptan and its metabolites M2 (as applicable) and M3 at specified timepoints
- Plasma concentration ratio of M2 (as applicable) to balovaptan and M3 to balovaptan
- Other PK parameters as appropriate

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of treatment with 10-mg equivalent dose balovaptan on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale (see Section 5.3.3)
- Incidence and severity of treatment-emergent abnormalities in physical and neurologic examinations
- Change from baseline in vital signs
- Change from baseline in ECG parameters
- Change from baseline in clinical laboratory test results

[redacted]

2.3 EXPLORATORY EFFICACY OBJECTIVE

The exploratory objective of this study is to make a preliminary evaluation of the clinical activity of balovaptan on the basis of the following endpoints:

- Change from baseline on the Vineland-II two-domain composite (2DC) score (defined as the mean of the Communication domain standard score and the Socialization domain standard score) at Weeks 6, 12, 24, and 54
- Change from baseline on severity of clinical impressions as measured using the Clinical Global Impressions-Severity (CGI-S) at Weeks 6, 12, 24, and 54
- Change from baseline on clinical impressions as measured using the Clinical Global Impressions-Improvement (CGI-I) at Weeks 6, 12, 24, and 54
- Change from baseline on severity of clinical impressions as measured using the Caregiver-Reported Global Impression of Change (CaGI-C) and Caregiver-Reported Global Impression of Severity (CaGI-S) at Weeks 6, 12, 24, and 54

2.4 ADDITIONAL OBJECTIVE

An additional exploratory objective for this study is to evaluate the palatability of balovaptan in subjects 2–4 years old on the basis of the following endpoint:

- Palatability test of study drug given after administration of balovaptan at Week 6

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib, multicenter, open-label study in children 2–4 years old with ASD to investigate the pharmacokinetics, safety, and tolerability of an oral dose of 4 mg balovaptan QD, which is predicted to *be adult-equivalent, i.e., provide a plasma exposure range that is comparable to that following oral doses of 10 mg balovaptan QD in adults*. The study consists of a 6-week treatment period to evaluate the pharmacokinetics of balovaptan in 2- to 4-year old children followed by an optional extension period of 48 weeks.

Subjects for whom consent has been provided by their parent or legal guardian will undergo screening within 4 weeks prior to the first study drug administration. Eligible subjects will be enrolled in an open-label fashion and treated with 4 mg balovaptan.

The safety of balovaptan will be assessed by monitoring of adverse events, serious adverse events, clinical laboratory values, ECGs, physical and neurologic examinations, and safety outcome assessments such as suicidality. Exploratory efficacy endpoints will examine core autism symptoms (social interaction, social communication) and functional deficits.

The total duration of the study (from screening through to study completion) for each subject will be approximately 12 weeks or 60 weeks, depending on whether or not he or she participates in the optional extension period, divided as follows:

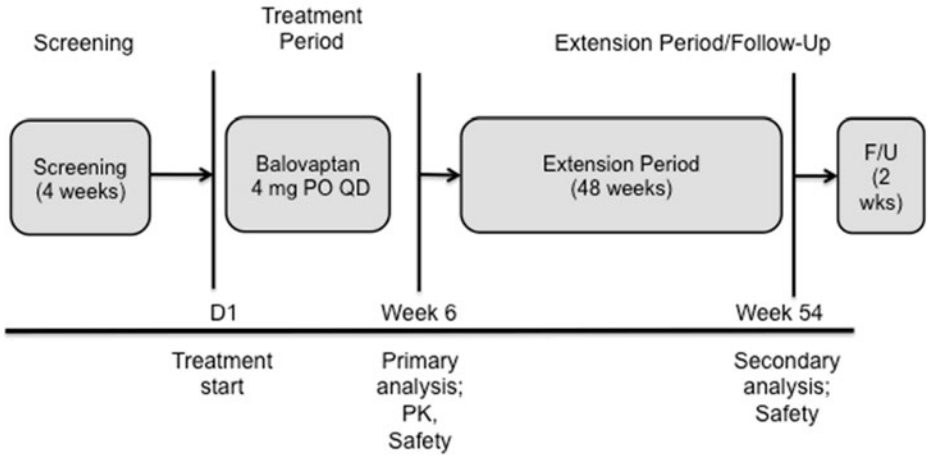
- Screening period: approximately 4 weeks
- Treatment period: 6 weeks
- Optional extension period: 48 weeks
- Post-treatment follow-up period: 2 weeks

Approximately 10 subjects will be enrolled at approximately 10 international sites, including sites in North America and Spain. A subject may be replaced in the event that the subject's treatment is discontinued for any reason during the 6-week treatment period.

Enrollment will be based on the selection of two age groups (children 3–4 years old vs. children 2 years old). The targeted ratio between the age groups will be approximately 2:1 (children 3–4 years old to children 2 years old; e.g., 7 children 3–4 years old and 3 children 2 years old if 10 subjects are enrolled). This ratio may change based on the ability to recruit children in both age groups and based on observed exposures levels of balovaptan and its metabolites.

An overview of the study design is depicted in Figure 1. A schedule of activities for the 6-week treatment period is provided in [redacted], a schedule of activities for the optional extension period is provided in [redacted], and a schedule for collection of PK samples is provided in [redacted].

Figure 1 Study Schema



F/U=follow-up; PK=pharmacokinetic; PO=orally; QD=once a day; wks=weeks.
Note: All subjects will return for a follow-up visit 2 weeks after their final dose of study drug.

3.1.1 Screening Period

Subjects whose parent or legal guardian has given their consent for the subject to participate in the study will undergo a screening procedure within 4 weeks before the first study drug administration (Day 1). Subjects must meet all of the eligibility criteria in order to qualify for the study (see Sections 4.1.1 and 4.1.2).

In cases in which the screening laboratory samples are rejected by the central laboratory (e.g., a hemolyzed sample) or if the results are not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated within the screening period. If retesting is not possible within the 4-week screening window, the screening period may be prolonged but should not exceed 6 weeks. It should also be verified that the subject continues to meet all other eligibility criteria.

Specific samples for laboratory tests and assessments at baseline do not need to be repeated if the baseline visit occurs within 2 weeks after the screening visit and no clinically relevant abnormal results have been identified at screening and no clinical abnormalities have emerged since screening that require mandated laboratory assessments in the opinion of the investigator (see [redacted]).

[redacted]

[redacted]

3.1.2 Re-Screening

In certain cases, subjects not meeting the eligibility criteria can be re-screened once and uncertainties can be discussed with the Medical Monitor or designee.

Screen-failed subjects can only be re-screened if there is a substantial change in the subject's general condition (e.g., prohibited medication was stopped or weight loss) and if recruitment for the study is still ongoing. Re-screening will not be allowed if the subject failed to meet the disease-specific inclusion criteria (e.g., Autism Diagnostic Observation Schedule™, Second Edition [ADOS-2]).

Abbreviated re-screening (written informed consent, medical history, physical examination, fasted laboratory safety, coagulation, serology, urinalysis, inclusion/exclusion criteria) may be allowed under circumstances where the subject is screen-passed but could not be assigned to treatment within the screening window due to a study halt or to logistical, personal, or technical reasons. At no time should the duration between the original screening visit and the abbreviated re-screening visit exceed 3 months. Abbreviated re-screening will only be permitted in cases where this poses no safety risk to the subject and if recruitment for the study is still ongoing.

Safety laboratory tests that would exclude the subject at screening may be repeated once (as unscheduled laboratory tests) if it is suspected that the abnormal result is transient and likely to be normal at repeat.

3.1.3 Six-Week Treatment Period

All subjects will receive 6 weeks of treatment with an oral dose of 4 mg of balovaptan QD, which is predicted to be equivalent to the adult oral dose of 10 mg balovaptan QD. Study enrollment will occur only after a subject has met all eligibility criteria. At the baseline visit (Day 1), subjects will undergo a series of assessments outlined in the schedule of activities (see [redacted]).

The target exposure range for a 10-mg equivalent dose is based on the observed exposure distribution in adults receiving 10 mg balovaptan QD in Study BP28420, with a median $AUC_{\tau,ss}$ of approximately 1000 ng•hr/mL, interquartile range of approximately 700–1400 ng•hr/mL, and 90% of $AUC_{\tau,ss}$ values (5th–95th percentile) within approximately 400–2000 ng•hr/mL.

For the first subject, if the $AUC_{\tau,ss}$ is $>$2000ng•hr/mL or $<$400 ng•hr/mL, then the dose will be adjusted with the aim to get $AUC_{\tau,ss}$ as close as possible to the target 1000 ng•hr/mL. Any new subject to be enrolled will receive this adjusted dose, unless cumulative data from all subjects in the study indicate that further dose adjustments are required to be within the target distribution. If required based on accumulating PK data,

the dose may be adjusted further. It is planned that any dose change will be implemented for all enrolled subjects and any additional enrolled subjects. However, if indicated based on large variability in the systemic exposure of balovaptan, different doses may potentially be given for children of different ages or adjustment of dose may potentially be done for a given individual subject so that plasma exposures are not outside the targeted range for an extended period of time. Subjects should come to the site for an unscheduled study visit as soon as possible after a dose change is confirmed if subjects cannot receive the new study drug supply at the next regular study visit early enough or if any other relevant clinical, administrative, or operational reasons call for an additional study visit. The decision to change the dose will be made by the Sponsor and communicated to sites.

If treatment interruption occurs between Day 1 and Week 2 (the PK sampling visit), after consultation with the clinical pharmacologist, subjects may need to be withdrawn and replaced or the Week 2 PK visit may be delayed.

3.1.4 Optional Extension Period

All subjects who complete the 6-week treatment period, and in the view of the investigator, have not experienced relevant adverse events considered prohibitive for further treatment are eligible for participation in the extension period of the study. The transition into the extension period is seamless; subjects will continue to receive study drug treatment without interruption after the end of the 6-week period. Subjects who do not participate in the extension period of the study will complete the follow-up visit 2 weeks after their final dose (see Section 3.1.5).

The 48-week duration of the extension period serves to evaluate the long-term safety, tolerability, and exploratory efficacy of balovaptan treatment in young children with ASD. All subjects will continue to receive an oral dose of 4 mg balovaptan QD, which is predicted to be equivalent to the adult oral dose of 10 mg balovaptan QD. If a change in dose occurs, all subjects in the 6-week treatment period and all subjects in the extension period will receive the new dose at the earliest opportunity (see Section 3.1.3). For the schedule of activities to be performed during the extension period, see [redacted].

3.1.5 Follow-Up Period

In the case of treatment discontinuation during the 6-week treatment period or extension period, in order to continue to assess the safety and tolerability of balovaptan, subjects should return to the site 2 weeks after their final dose. Subjects who complete the 6-week treatment period but who do not enter the extension period and subjects who complete the extension period should also return to the site 2 weeks after their final dose for a follow-up visit.

3.1.6 Internal Monitoring Committee and Scientific Oversight Committee (IMC and SOC)

An IMC together with a SOC will review all available data on a regular basis per the IMC charter or on an ad-hoc basis if deemed necessary.

The IMC will comprise a selected subset of internal Roche representatives and the SOC members are independent experts external to Roche.

The IMC and SOC charters provides further details about the roles and responsibility of the IMC, identifying members, defining the timing of meetings, and communication of meeting discussion points.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study is defined as the date when the last subject, last visit occurs in the follow-up period. The end of the study is expected to occur 14 months after the last subject is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

It is anticipated that it may take up to 18 months to recruit all subjects for the study. Hence, the total length of the study from screening of the first subject to the end of the study is estimated to be approximately 2.5–3 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Open-Label Design

This study will evaluate the pharmacokinetics, safety, and tolerability of balovaptan in children ages 2–4 years with ASD to identify the dose for this age group for enrollment in subsequent efficacy trials. Drug concentrations in plasma are assumed to be objective measurements, which cannot be affected by volunteer or staff behavior. Therefore, it is generally accepted to conduct PK studies with an open-label design, without placebo treatments. Furthermore, an open-label, standalone study design was selected to ensure that the expected exposure is confirmed as quickly as possible. The extension period will also give subjects and their families the option to continue treatment with balovaptan, thereby balancing study burden with opportunity of possible benefit. Safety information will be collected and discussed in context of historical data available.

[redacted]

[redacted]

[redacted]

[redacted]

3.3.3 Rationale for Subject Population

The results of this study in children 2–4 years old will enable the Sponsor to include the age group in the upcoming pediatric Phase III program. Based on the current scientific understanding of autism and treatments of autism as well as based on preclinical and clinical results of treatment with balovaptan, the prospect of observing a clinically significant improvement in core autism symptoms with an early pharmacologic intervention appears to be plausible (see Sections 1.2 and 1.3).

Children diagnosed as early as 2–4 years old are often severely affected and have higher rates of medical comorbidities (Muskens et al. 2017). Potential comorbidities like metabolic, gastrointestinal (GI), or severe neurologic disorders could have a considerable impact on the pharmacokinetics of balovaptan and would also potentially lead to a higher rate of adverse events. Therefore, children with severe comorbidities and symptoms as well as symptoms that are highly indicative of the development of severe comorbidities in the future will be excluded from the study (see Section 4.1.2).

In children diagnosed before the age of 3, estimates of diagnosis stability are more variable, with results ranging from 54% to 100%. In a review by Woolfenden et al. (2012), four of the 11 studies reviewed of children diagnosed with autistic disorder or ASD younger than 3 years old reported a 100% stability rate, and two studies reported rates <70%. However, although both increases and decreases in ASD severity have been noted during follow-up periods from 2 to 4 years, the overwhelming majority of children retain what would be considered ASD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5].

The predictive value of diagnostic tools for toddlers and patterns of symptom change are important considerations for clinicians making early diagnoses. To ensure the highest specificity for recruitment of children meeting full diagnosis criteria for ASD and to avoid recruiting children whose diagnosis may change over the following years, the ADOS-2 is deployed for confirmation of diagnosis in this study. For enrollment in this study, the DSM-5 criteria for diagnosis of autism need to be met with highest confidence in the opinion of the investigator. Children with ambiguous diagnostic results cannot be enrolled in the study.

As noted above, balovaptan at the intended dose has been shown to be well tolerated and safe in the clinical program to date, and the juvenile toxicity studies in rats and dogs did not reveal a higher susceptibility to any toxicity compared with toxicology studies in adult animals.

3.3.4 Rationale for Extension Period

The study will include an optional 48-week extension period to evaluate effects of balovaptan in young children over a longer time period. The extension period of 48 weeks will give subjects and their families the option to continue treatment with balovaptan and will add to the long-term safety information as well as provide the first, preliminary indicators of efficacy of balovaptan in this age group.

4. MATERIALS AND METHODS

4.1 SUBJECTS

Based on the first observed exposure levels of balovaptan and its metabolites approximately 10 children are expected to be enrolled in the study.

4.1.1 Inclusion Criteria

Subjects must meet the following criteria for study entry:

- Parent or legal guardian/representative willing and able to give written informed consent according to local requirements and subject willing and able to provide informed assent or consent according to local requirements
- Males or females 2–4 years of age at the time of signing Informed Consent Form
- Diagnosis of ASD according to DSM-5 criteria for ASD

  Diagnostics will be performed by a team of autism experts and confirmed by ADOS-2 criteria. The DSM-5 criteria for diagnosis of autism must be met with the highest confidence in the opinion of the investigator. Children with ambiguous diagnostic results cannot be enrolled in the study.

  If the ADOS-2 assessment has been performed by a certified rater and documented within 12 months of the screening visit, *it is not mandatory to repeat it unless the subject was assessed below an age of 2 years.*
- Hearing and vision compatible with the study assessments, as judged by the investigator

- Ability for subject and the caregiver to comply with the study protocol, in the investigator's judgment
- Availability of a parent or other reliable caregiver who is fluent in language of the site and has frequent and sufficient contact with the subject

  The same person should accompany and agree to provide information about the subject's behavior and symptoms at the baseline and Week 6, 12, 24, and 54 visits.

4.1.2 Exclusion Criteria

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

4.1.2.1 Neurologic and Psychiatric Exclusion Criteria

Subjects who meet any of the following neurologic and psychiatric exclusion criteria will be excluded from study entry:

- Clinically significant psychiatric and/or neurologic comorbidity that may interfere with the safety or efficacy endpoints in the view of the investigator
- Clinically significant regression of any acquired language and motor function skills in the opinion of the investigator throughout the subject's development
- History of seizures with the exception of a single, non-complicated febrile seizure ≥6 months before screening
- Clinical diagnosis of peripheral neuropathy or signs and symptoms indicative of peripheral neuropathy

4.1.2.2 Cardiovascular Exclusion Criteria

Subjects who meet any of the following exclusion criteria related to cardiovascular disorders will be excluded from study entry:

- Any clinically relevant cardiovascular disease
- Confirmed elevation in cardiac troponin I (cTn I), high-sensitive cardiac troponin T (hs cTn T), N-terminal pro–B-type natriuretic peptide (NT-proBNP) or, if conducted, clinically relevant abnormality in Doppler echocardiogram
- Confirmed (e.g., on two consecutive measurements) clinically significant abnormality on ECG at screening, including, but not limited to, a QT interval corrected through use of Fridericia's formula (QTcF) of ≥450 ms, absence of dominating sinus rhythm, or second- or third-degree atrioventricular block
- *Confirmed (e.g., on two consecutive measurements) systolic or diastolic blood pressure above the 95th percentile or below the 5th percentile according to the Centers for Disease Control and Prevention (CDC) norm tables referring to stature (height)-for-age percentiles (see [redacted]).*
- *Confirmed (e.g., on two consecutive measurements) heart rate:*
  >150 bpm in 2-year old children,
  >135 bpm in 3-year old children, or
  >120 bpm in 4-year old children.

4.1.2.3 Other Organ Systems Exclusion Criteria

Subjects who meet any of the following exclusion criteria related to other organ systems will be excluded from study entry:

- Concomitant disease or condition (pulmonary, GI, hepatic, renal, metabolic, immunological system) that could interfere with, or treatment of which might interfere with, the conduct of the study; or discontinuation of prohibited medication that might pose unacceptable risks to the subject in the opinion of the investigator
- Evidence for current GI disease that would interfere with the conduct of the study or pose unacceptable risks in the opinion of the investigator (e.g., GI bleeding, active stomach ulcer)
- History of coagulopathies, bleeding disorders, or blood dyscrasias
- Positive serology for HIV-1 or HIV-2
- Confirmed clinically significant abnormality in parameters of hematology, clinical chemistry, coagulation, or urinalysis, specifically a confirmed ANC $<$ LLN

  Children with confirmed CPK elevations exceeding 2 $\times$ ULN will be excluded
- History of malignancy

4.1.2.4 Additional Exclusion Criteria

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

- Participation in an investigational drug study within 90 days (or 5 times the half-life of the investigational molecule, whichever is longer) prior to treatment assignment, or participation in a study testing an investigational medical device within 90 days prior to treatment assignment or if the device is still active
- Presence of any clinically significant abnormality likely to interfere with the conduct of the study according to the judgment of the investigator
- Clinically significant loss of blood within 3 months prior to screening
- Unstable use of permitted medications for 4 weeks before screening (see Section 4.4.2)
- Use of prohibited medications within 30 days (or 5 times the half-life, whichever is longer) prior to initiation of study treatment (see Section 4.4.4)
- Other severe medical comorbidity that may interfere with the safety or efficacy endpoints

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a single-arm and open-label study with no randomization or stratification factors. If a subject is confirmed as eligible at the baseline visit, the investigator or designated person will register them in the interactive voice or web-based response system (IxRS), and the subject will be allocated a unique number and assigned to the confirmed dose of balovaptan.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is balovaptan.

[redacted]

4.3.2 Study Treatment Dosage, Administration and Compliance

The treatment regimens are summarized in Section 3.1.

Refer to the Balovaptan Investigator's Brochure for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for treatment interruption or discontinuation for subjects who experience adverse events are provided in Section [redacted].

Balovaptan will be supplied as dispersible tablets and should be taken once per day in the morning with or without food. If administration of study drug in the morning is not possible for the subject, the study drug should be taken regularly at another time of the day. The dispersible tablets will be dispersed in approximately 5 mL of water, orange or apple juice, or milk using a provided cup (for more details please refer to the "Instructions for use"). Subjects will receive a total daily dose approximately equivalent to the adult dose of 10 mg balovaptan QD in terms of predicted exposure.

The first dose of the study medication will be administered on Day 1 after all predose baseline assessments have been conducted.

Subjects will arrive at each study visit without having taken their daily dose of study drug. Following collection of the predose assessments, subjects will take their daily dose of study drug. Site staff will record the actual date and time of the dose intake.

At Week 2 when postdose PK blood samples are taken, the exact time at which the treatment was administered and whether the subject was in a fasted or fed state *is*

recorded. Fasted and fed states refer to windows of 2 hours before and 2 hours after study drug administration, respectively. A fed state is considered as having eaten an amount of food that can be regarded as a meal (e.g., breakfast).

At all visits, it will be recorded in the eCRF if *study drug* administration took place with or without food. *Administration with food refers to study drug administration when food is consumed within 30 minutes before dosing. T*he timing of dosing on the 2 days before a study visit with *postdose* PK-sampling and whether the subject was in fasted or fed state will *also* be collected *in the caregiver diary.*

Subjects should not take balovaptan in the following circumstances:

- Delay in drug administration and next regular intake would occur in less than 12 hours
- Partial drug intake (e.g., if the subject disgorges part of the study drug)

  If the study drug was *not* taken *or* only partially *taken* on *any of the 2* days *prior to* a study visit with PK sampling, the study visit and PK sampling should be delayed to within the next *4 days*. In addition, if partial drug intake occurs after the *predose (*trough*)* PK collection at Week 2, the predose and postdose PK collection should likewise be *taken at a* delayed *visit within the visit window.*

Compliance regarding administration of study medication at home will be monitored by the completion of a diary card by the subject's caregiver. Diary cards will be reviewed at each clinic and home visit *but it is recommended that study site staff contact the caregiver regularly between visits to check on compliance and diary card entries.*

4.3.3 Investigational Medicinal Product Accountability

The IMP required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS, to confirm the shipment condition and content. Any damaged shipments will be replaced.

The investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. The Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the subject to whom the study drug was dispensed (e.g., subject's initials and date of birth)
- The date(s) and quantity of the study drug dispensed to the subject
- The date(s) and quantity of the study drug returned by the subject
- All records and drug supplies must be available for inspection by the Roche Monitor (at every monitoring visit)

IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate

documentation. The site's method of destroying Sponsor-supplied IMP 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. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed, and provided that adequate storage and integrity of drug has been confirmed.

The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Written documentation of destruction must contain the following:

- Identity (batch numbers or study subject numbers) of investigational product destroyed
- Quantity of investigational product destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person (or company) who destroyed investigational product

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

Unused study drug from the site that has not been stored properly should not be destroyed until the final report has been approved. If there are any issues with the drug it should be returned to the appropriate Roche clinical trial supplies department for long-term storage and not destroyed.

4.3.4 Continued Access to Balovaptan

Currently, the Sponsor does not have any plans to provide Roche IMP (balovaptan) or any other study treatments to subjects who have completed the study. The Sponsor may evaluate whether to continue providing balovaptan in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

Subjects will receive balovaptan as part of the optional extension period, provided they have completed the first 6 weeks of treatment, as described in Section 3.1.4.

4.4 CONCOMITANT THERAPY

The addition of a new medication or a change in the dose of a medication after signing the Informed Consent Form should only occur for the treatment of an adverse event.

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements, and any non-medicinal interventions, such as early intervention programs) used by a subject 12 weeks prior to screening until the follow-up visit.

All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. All therapy and/or medications administered to manage adverse events should be recorded on the Adverse Event eCRF.

4.4.1 Non-Pharmacological Interventions

Individuals and their families that are participating in this trial should continue any local standard-of-care therapies, early intervention programs, parent training, and/or community services interventions that have been made available to them. No family should refrain from starting or continuing such therapies to be able to take part in this study or continue study participation.

4.4.2 Permitted Pharmacological Therapy

It is not expected that subjects enrolled in this trial will be taking psychiatric medications upon entering the trial. Psychotropic medication is allowed if permitted by the Medical Monitor or designee. All medications to treat other coexisting symptoms and medical conditions should be documented on the eCRF and continued at a stable frequency and dosage from screening through the completion of the trial; any changes should be reported on the appropriate eCRF.

Examples of allowed medications include the following:

- Melatonin
- Folic acid

4.4.3 Cautionary Pharmacological Therapy

There is a potential for a drug-drug reaction between balovaptan and oral medications that are clinically relevant substrates of P-glycoprotein (P-gp), particularly those with a narrow therapeutic window (e.g., loperamide). However, the risk is predicted to be small when balovaptan is administered $\geq$5 hours prior to a P-gp substrate.

4.4.4 Prohibited Pharmacological Therapy and Food Products

The following therapies are not allowed during the study and must be stopped 30 days prior to screening or 5 times the half-life prior to treatment assignment (whichever is longer) to ensure washout of medication:

- Strong and moderate inhibitors and inducers of CYP3A4
- Quinidine (a P-gp substrate)
- Chronic adrenocorticoid or glucocorticoid use (use of inhaled or topical formulations are allowed)
- Oxytocin
- Desmopressin acetate
- Bumetanide
- Agents inhibiting vasopressin receptors (e.g., tolvaptan, conivaptan)
- Hematotoxic drugs requiring frequent hematologic monitoring of WBCs (e.g., clozapine)
- Herbal therapies, vitamins and other dietary supplements (unless allowed by the Medical Monitor or designee)
- Use of any concomitant psychotropic medication (unless allowed by the Medical Monitor or designee)
- Use of any concomitant medication known to potentially cause peripheral neuropathy per the Warnings and Precautions section of the U.S. label or the corresponding section of the local label

Medications and Food Products Prohibited due to Effects Related to Cytochrome P450 Enzymes

In vitro data suggest that balovaptan is metabolized through CYP3A4 and there is a potential for drug-drug interaction with any medication, herbal therapy, or food product that strongly inhibits or induces this enzyme. Therefore, the following medications, herbal therapies, and food products are prohibited:

- All moderate and strong inhibitors of CYP3A4 (e.g., oral ketoconazole, clarithromycin, grapefruit juice, erythromycin, ciprofloxacin, diltiazem)
- All inducers of CYP3A4 (e.g., carbamazepine, phenytoin, St. John's wort, and modafinil)

The above lists of medications/herbal therapies/food products are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study drug. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

The schedules of activities for the 6-week treatment period and optional extension period are provided in [redacted] and [redacted], respectively. The schedule for PK samples is provided in [redacted]. All activities should be performed and documented for each subject.

4.5.1 Informed Consent Forms and Screening

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

All screening evaluations must be completed and reviewed to confirm that subjects meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details regarding 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 and surgeries will be recorded at screening. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the subject within 12 weeks prior to the screening visit as well as details of psychosocial and non-pharmacological interventions used over the past years will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

The medical history will also contain information about pregnancy, birth, and neonatal period of the subject.

Demographic data will include age, sex, and self-reported race/ethnicity. Caregivers will also be asked about the subject's residential setting, school and preschool, day care facilities, level of education, participation in educational or day programs, and any non-medical hospitalizations.

General information will also be collected on the caregiver who will oversee the subject's adherence with protocol-specified procedures and study drug, and report on the subject's status. This will include, for example, the caregiver's relationship to the subject, the amount of time the caregiver spends with the subject, and whether the caregiver lives at the same residence.

4.5.3 Physical and Neurologic Examinations

At the timepoints listed in the schedules of activities (see [redacted] and [redacted]), a complete physical examination will be performed and should include an evaluation of the head, eyes, ears, nose, throat, neck, and lymph nodes and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, and neurologic systems. The physical examination will not include pelvic, rectal, or breast examinations.

Limited, symptom-directed physical examinations should be performed as clinically indicated. Changes from baseline abnormalities should be recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

At all timepoints listed in the schedules of activities (see [redacted] and [redacted]), a neurologic examination will be performed and should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, coordination, as well as an examination for symptoms of peripheral neuropathy (see [redacted] and Section [redacted]). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF and carefully evaluated in terms of eligibility of the subject for enrollment in this study.

Complete physical and neurologic examinations need to be performed by an examiner with substantial experience in pediatric neurology and experience in examining young children. Based on a child's developmental age, individual capabilities as well as autistic symptoms (e.g., attention span, sensory symptoms, irritability) it is expected that the children will often not be able to be examined in all described evaluation areas.

Body height, weight, and head circumference will be recorded as specified in [redacted] and [redacted]. *Head circumference will be only measured up to 3 years of age given the availability of CDC published nomograms.* Body mass index (BMI), including age- and sex-specific BMI percentiles relevant for inclusion, will be derived at screening. These anthropometric parameters will be determined according to Centers for Disease Control and Prevention (CDC) BMI Percentile Calculator for Child and Teen (https://www.cdc.gov/healthyweight/bmi/calculator.html). Screenshots of this derivation will be kept in the source data.

[redacted]

4.5.4 Vital Signs

Vital signs will include measurement of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the subject is ideally in a seated position, and body temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Temperature Measurements

Temperature will be measured at site visits as part of the vital signs assessment (see Section 4.5.4 and [redacted] and [redacted]).

Body temperature measurements should be taken by the caregiver, at home, once every 2 weeks, at a similar time of the day for the first 30 weeks. Temperature measurements taken at home should be performed using the tympanic thermometer, supplied by the Sponsor, in an indoor environment at room temperature and recorded. Site personnel should train the caregiver on the correct use of the thermometer and the importance of compliance with the procedure. The tympanic thermometer should be returned to site at the end of the subject's study participation.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Laboratory and biomarker samples will be collected at the timepoints specified in the schedules of activities (see [redacted] and [redacted]).

Additional blood or urine samples may be obtained 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. When the clinical significance of abnormal laboratory results is considered uncertain, screening laboratory tests may be repeated before treatment assignment to confirm eligibility.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and sent to the central laboratory for testing. Abnormal results should be followed until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)

- Serum chemistry panel: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, CPK, total protein, albumin, total and direct bilirubin, ALP, ALT, AST, LDH, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Thyroid function and glycated hemoglobin testing: glycated hemoglobin (HbA_{1c}), thyroid-stimulating hormone (TSH), and free thyroxine (also known as T4)

[redacted]

- Coagulation: INR, aPTT, and PT
- Viral serology: HIV
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)

  Urinalysis will be performed only if feasible for the subject based on their ability to give a urine sample. If there is a clinically significant positive blood or protein result, the urine sample will be sent to the central laboratory for microscopy and culture.
- Plasma samples for PK analysis (see [redacted])

  Plasma concentrations of balovaptan and its metabolites M3 and M2 (as applicable) will be determined using a specific and validated liquid chromatography-tandem mass spectrometry method. Other balovaptan-derived metabolites in plasma may be investigated as appropriate using an exploratory method.
- Unscheduled visit laboratory assessments

  Repeat testing of laboratory parameters listed above or measurement of additional laboratory parameters may be undertaken to interpret any adverse events or abnormal hematologic or chemistry finding. Depending on the adverse event, additional PK samples may also be taken. Decisions regarding unscheduled laboratory assessments will be made by the investigator and in consultation with the Medical Monitor and external experts if necessary.

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

- Capillary blood samples for hematology

[redacted]

For all subjects, if venipuncture is not feasible in the opinion of the investigator at specific timepoints noted in the schedules of activities (see [redacted] and [redacted]), the venous blood hematologic sample can be replaced by capillary blood sampling for analysis of ANC.

- Capillary blood samples for selected serum chemistry (sodium, potassium, creatinine, total and direct bilirubin, ALP, ALT, AST, and CPK)

  For all subjects for whom venipuncture appears not to be feasible at that visit in the opinion of the investigator, venipuncture can be replaced by capillary blood sampling.

  [redacted]

Per the schedules of activities ([redacted] and [redacted]), the total blood volume taken per individual in this study will not exceed 1% at any single visit or 3% of the total blood volume during a 4-week period. (The total volume of blood is estimated at 80–90 mL/kg body weight.) Please note that unscheduled visits or losses during the maneuver may increase the blood volume. If there is uncertainty with regard to the total blood volume to be collected at any timepoint, the Medical Monitor or designee should be contacted.

If the available blood volume from venous blood sampling is insufficient for all scheduled laboratory tests, the blood sample prioritization below should be followed.

1. PK
2. Hematology
3. [redacted]
4. Serum chemistry
5. Coagulation
6. Thyroid function testing
7. Viral serology

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

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma samples collected for PK analysis may be needed for PK assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a subject is withdrawn from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the subject's parent or legal guardian 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.

4.5.7 Palatability Test

Palatability (taste and acceptability) testing of the dispersible tablet formulation of the study drug will include questions directed to the caregiver to capture subjective experiences with the dispersible tablets. Furthermore, the input of the caregiver will also be sought to aid interpretation of the experience or reaction of the subjects.

Palatability assessment will be performed at the timepoint specified in the schedule of activities [redacted] after administration of study drug.

4.5.8 Electrocardiograms

At baseline, ECGs will be recorded in triplicate, if feasible. Single ECG recordings will be obtained at specified timepoints, as outlined in the schedules of activities (see [redacted] and [redacted]), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the subject has been resting in a supine position for at least 5 minutes if feasible. All ECGs are to be obtained prior to other procedures scheduled at the same time (e.g., vital sign measurements, blood draws) and should ideally not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during the ECG recording if feasible.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the subject's permanent study file at the site. Digital recordings will be stored at a central ECG laboratory. The following parameters will be provided as non-eCRF data: heart rate, RR interval, QRS interval, pulse rate duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings or, if considered appropriate by the Sponsor, ECGs may be analyzed at a central laboratory.

If at a particular postdose timepoint the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 60 minutes, and ECG monitoring should continue until QTcF has stabilized on two

successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section [redacted]. The investigator should also evaluate the subject for potential concurrent pro-arrhythmic risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

[redacted]

[redacted]

[redacted]

[redacted]

4.5.10 Requirements for Caregivers

The caregiver must live with the subject or have substantial and sufficient periods of contact with the subject and be willing and able to attend the on-site visits when required. The caregiver must oversee the subject's adherence with protocol-specified procedures and study drug dosing (see Section 4.3.2), and report on the subject's status by means of completion of caregiver-reported/completed study assessments.

All disease-specific assessments will take place on site at the clinic. The same caregiver will provide feedback on all informant-based assessments throughout the study as established at baseline, and the same caregiver should accompany the subject to the visits at baseline, Weeks 6, 12, 24, and 54, and early termination. If a caregiver visit cannot be completed as arranged (e.g., the caregiver is delayed in transit), visits should be rescheduled as soon as possible after the original appointment. Caregiver-reported/completed assessments cannot be conducted over the telephone. A change of the reporting caregiver initials will be captured on the eCRF at all assessments.

4.5.11 Clinical Outcome Assessments

Observer-reported outcome (ObsRO) and clinician-reported outcome (ClinRO) instruments will be completed. ObsRO data will be collected through use of the following instruments: Vineland-II, CaGI-C, and CaGI-S. ClinRO data will be collected through use of the following instruments: Vineland-II, ADOS-2, CGI-I, CGI-S, and Columbia-Suicide Severity Rating Scale (C-SSRS). The ADOS-2 will be administered only at screening. The other instruments should be administered as per the schedules of assessments (see [redacted] and [redacted]) and in the order shown in Table 1.

Table 1 Sequence of Scale Administration

Order	Scale	Respondent(s)	
1	Vineland-II	Caregiver	Qualified rater
2	C-SSRS	Caregiver	Qualified rater
3	CaGI-S	Caregiver	—
4	CaGI-C	Caregiver	—
5	CGI-S	—	Qualified rater
6	CGI-I	—	Qualified rater

CaGI-C = Caregiver-reported Global Impression–Change; CaGI-S = Caregiver-reported Global Impression–Severity; CGI-I = Clinical Global Impressions of Improvement; CGI-S = Clinical Global Impressions of Severity; C-SSRC = Columbia-Suicide Severity Rating Schedule; Vineland-II = Vineland™ Adaptive Behavior Scales, Second Edition.

4.5.11.1 Data Collection Methods for Clinical Outcome Assessments

ObsRO instruments will be administered at the clinic at specified timepoints during the study (see schedules of activities in [redacted] and [redacted]). At the clinic, instruments will be administered before the observer receives any information on disease status, prior to the performance of non-ObsRO assessments, and prior to the administration of study treatment, unless otherwise specified.

ObsRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. A backup device will be provided to each site in the event of device issues. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

During clinic visits, ObsRO instruments should be administered as outlined below:

- Subjects' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor.
- Sites should allow sufficient time for observers to complete the instruments, estimated to be from 0–70 minutes, depending on the visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Observers should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Observers should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

ClinRO instruments will be completed at the clinic at specified timepoints during the study (see the schedules of activities in [redacted] and [redacted]). ClinRO instruments will be administered after any ObsRO measures and prior to the administration of study treatment. The instruments will be completed through use of an electronic device provided by the Sponsor. Clinicians must complete the official version of each ClinRO instrument, as provided by the Sponsor. The data will be transmitted to a centralized database maintained by the electronic device vendor.

Rater qualification for specific-outcomes assessments, including, but not limited to, the Vineland-II and ADOS-2 will be reviewed per the criteria established by the Sponsor. Only raters confirmed by the vendor to be qualified on those assessments should rate in this study.

If the same qualified rater is not available within the visit window, delaying the visit is preferred to changing the rater. The same rater or clinician will perform the Vineland-II together with the same caregiver throughout the study as established at the baseline visit.

4.5.11.2 Description of Clinical Outcome Assessment Instruments

Vineland™-II Adaptive Behavior Scales, Second Edition

The Vineland-II is an instrument that measures communication, daily living skills, socialization, maladaptive behavior (not assessed in this study), and motor skills (Sparrow et al. 2005). The Vineland-II will be administered by a qualified rater at the clinic as a semi-structured interview of the caregiver, during which the rater will ask the caregiver open-ended questions relating to the subject's activities and behavior.

Standardized domain scores will be obtained for the individual domains of Socialization, Communication, Motor Skills and Daily Living Skills. Standardized scores range from 20 to 160 with a mean of 100 and standard deviation of 15. Higher scores indicate better adaptive behavior skills. The Vineland-II 2-DC is calculated as the arithmetic mean of the Socialization standard score and Communication standard score.

The interview will take approximately 45–60 minutes to complete and will be audio recorded.

Autism Diagnostic Observation Schedule, Second Edition

The ADOS-2 is a diagnostic tool used to document the presence of ASD (Lord et al. 2000; Gotham et al. 2007). During a semi-structured evaluation, the individual is observed in a naturalistic social situation and assessed across areas of social communication, imagination, and restricted and/or repetitive behaviors.

The ADOS-2 includes modules for use with different age groups and language levels. The appropriate module of the ADOS-2 will be administered by a certified rater to subjects at the clinic at screening. Scores range from 1 to 10 once the algorithm is applied, with higher scores indicating greater severity of ASD symptoms.

Clinical Global Impression–Improvement

The CGI-I is a single-item, clinician-rated measure, assessing the clinician's impression about changes in the subject's condition, in this case, ASD (not other conditions or comorbidities), compared with baseline.

The CGI-I utilizes a 7-point response scale, ranging from "very much improved" (1) to "very much worse" (7).

Clinicians should make a judgment on any changes from baseline based on the totality of information available to them (e.g., insights from subject and/or caregiver, information captured during the completion of other trial assessments).

The assessment will take up to 5 minutes to complete.

Clinical Global Impression–Severity

The CGI-S is a single-item, clinician-rated measure, assessing the clinician's impression of the severity of a subject's condition, in this case, ASD (not other conditions or comorbidities).

The CGI-S utilizes a 7-point response scale, ranging from "normal, not at all ill" (1) to "among the most extremely ill subjects" (7).

Clinicians should make a judgment on a subject's severity based on the totality of their experience of the population.

The assessment will take up to 5 minutes to complete.

Caregiver Global Impression–Change

The Caregiver Global Impression–Change (CaGI-C) is a 5-item, informant-based measure assessing the caregiver's impression about changes in subject's communication skills, social skills, daily living skills, and overall ASD compared with baseline.

The CaGI-C items utilize a 7-point response scale, ranging from "very much improved" (1) to "very much worse" (7). Each item is scored independently.

There is also an item asking about the importance any of the changes they have observed during the study.

The assessment will take up to 5 minutes to complete.

Caregiver Global Impression–Severity

The Caregiver Global Impression–Severity (CaGI-S) is a 4-item, informant-based measure, assessing the caregiver's impression about the severity of impairment of the subject's communication skills, social skills, daily living skills, and overall ASD during the preceding 7 days.

The CaGI-S items utilize a 5-point response scale, ranging from "no difficulty" (1) to "extreme difficulty" (5). Each item is scored independently.

The assessment will take up to 5 minutes to complete.

Columbia–Suicide Severity Rating Scale

The assessment of suicidality in clinical trials is a requirement for CNS-active molecules requested by health authorities.

The C-SSRS (http://www.cssrs.columbia.edu) is a clinician-rated tool recommended by health authorities including the U.S. Food and Drug Administration (FDA) to assess previous suicidality of a subject at screening (C-SSRS screening to be used at screening) as well as any new instances of suicidality during the clinical study (C-SSRS since last visit; to be used at subsequent visits). The C-SSRS incorporates a structured interview to prompt recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality.

An age-specific version of the C-SSRS will be used for children and this version will be applied in those children being at least 3 years old at baseline or after having turned to an age of 3 years during the study. No suicidality assessment will be performed for children younger than 3 years old.

After completion of the pediatric C-SSRS questionnaire, the investigator will ask the following additional questions relating to the areas of suicidal ideation, suicidal behavior, and self-injurious behavior (verbal or behavioral manifestations):

- Suicidal ideation: Has the child wished he or she were dead or wished he or she could go to sleep and not wake up?
- Suicidal behavior: Has the child made a suicide attempt? Has he or she done anything to harm himself or herself?
- Self-injurious behavior: Has the child engaged in non-suicidal self-injurious behavior?

If the investigator concludes there is a risk for suicidality, the investigator must take care for further evaluation of the risk, which may involve local experts in the field of suicidality.

The assessment will take up to 10 minutes to complete.

4.5.12 Entry and Exit Questions

Caregivers will be asked an entry question at the baseline visit about which aspect of *ASD* the subject they support they would most like to see improve during the study *and any changes they observed/experienced during the study*. A follow-up exit question will be asked at Week 6 (only for subjects who do not enter the extension period) or Week 54 to document what changes, if any, caregivers observed during the study. Responses to these questions will be reported on the eCRF as pre-specified variables (entry question) and free text (exit question).

The assessment will take up to 2 minutes to complete.

4.6 TREATMENT, SUBJECT, STUDY, AND SITE DISCONTINUATION

An excessive rate of withdrawals (either because of subjects discontinuing study drug or withdrawal from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of subjects should be avoided and all efforts should be taken to motivate subjects to comply with all the study-specific procedures and to be followed until the end of the 6-week treatment period.

Every attempt should be made to keep subjects on study drug throughout the duration of the trial.

Before permanently discontinuing study drug (either initiated by the subject's parent or legal guardian or the investigator), an interruption should be considered. Subjects, who temporarily discontinue study drug for any reason, should restart as soon as medically justified in the opinion of the investigator.

The investigator should show due diligence and explore all possible options to reach a subject who fails to return for a visit. The site must document all attempts to try to

contact the subject's parent or legal guardian in the subject's medical records and source documents.

In order to avoid loss to follow-up, the investigator should ask the caregiver at the study start for the contact details of a relative or friend who can be contacted in case the caregiver cannot be reached.

Subjects should not be withdrawn from follow-up unless a subject's parent or legal guardian explicitly withdraws consent to be contacted. All efforts should therefore be made to minimize the number of parents or legal guardians who withdraw consent.

If premature withdrawal from the study occurs for any reason, the investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information in the subject's medical records and on the eCRF.

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
- *Subject experiences failure to thrive, worsening nutritional status, or significant food refusal in the opinion of the investigator.*

- Subject unable to continue to comply with study requirements

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Subjects who discontinue treatment during the 6-week treatment period may be replaced.

All subjects who withdraw or discontinue from the study treatment early will be asked to return as soon as possible (and within 1 week after their final dose of study drug) for an early termination visit. Two weeks after their final dose of study drug subjects will come to the site for a follow-up visit.

4.6.2 Subject Discontinuation from the Study

A subject's parent or legal guardian has the right to voluntarily withdraw the subject 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's parent or legal guardian withdrawal of consent
- Study termination or site closure
- Any medical condition that may jeopardize the subject's safety if he or she continues in the study as determined by the investigator or Sponsor
- In the best interest of the subject as determined by the investigator or Sponsor
- 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 a reason for subject discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a subject's parent or legal guardian requests that the subject be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Subjects who are withdrawn from the study may be replaced.

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 adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event 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 Sections 5.3.5.8 and 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)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the Investigator, places the subject at immediate risk of death)

  This does not include any adverse event 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 adverse event 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 adverse event (e.g., rated as mild, moderate, or severe; 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 adverse event recorded on the eCRF.

Serious adverse events 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).

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

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

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

- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

[redacted]

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (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 adverse event 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 adverse events at each subject contact. All adverse events, 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.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events 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 serious adverse events.

After initiation of study drug, all adverse events will be reported until 6 weeks after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event 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 adverse event 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 3 provides guidance for assessing adverse event severity.

Table 3 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 or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- 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 re-introduction 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

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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 adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events 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 adverse event that is separated in time from the initiating event should be recorded as independent events 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 GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three 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 adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. 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 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 serious adverse events.

A recurrent adverse event is one that resolves between subject evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event 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 adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

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, along with a descriptor indicating if 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 adverse event. 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 5.3.5.3 for details on recording persistent adverse events).

[redacted]

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event 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 adverse event.

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.

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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$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 adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$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 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event 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 adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 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 adverse event 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").

5.3.5.9 Worsening of Autism Spectrum Disorder

Medical occurrences or symptoms of deterioration that are anticipated as part of ASD should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of symptoms related to ASD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of autism).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event 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 adverse event or a serious adverse event:

- Hospitalization for respite care
- 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 suffered an adverse event
- Prolonged hospitalization due to lack of home care facilities, caregiver issues, transport issues, and so on.

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

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

5.3.5.11 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (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
- Intentional overdose: intentional 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.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the subject, drug misuse could involve the drug being administered to someone other than the subject.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event 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 adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with balovaptan, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.

- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the subject: Enter the drug name and "subject supplied drug to third party" as the event term. Check the "Drug misuse" box.

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

5.3.5.12 Observer-Reported Outcome Data

Adverse event reports will not be derived from ObsRO data by the Sponsor, and safety analyses will not be performed using ObsRO data. Sites are not expected to review the ObsRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (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)

For serious adverse events and adverse events of special interest, 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 serious adverse events to the local health authority and Institutional Review Board/Ethics Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor/Roche Medical Responsible:	[redacted], M.D. (Primary)
Mobile Telephone No.:	[redacted]
Medical Monitor:	[redacted] (Secondary)
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Medical Monitor:	[redacted], *M.D. (Tertiary)*
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 serious adverse events 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, serious adverse events and adverse events of special interest will be reported until 2 weeks after the final 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 Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, 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. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >2 weeks after the final dose of study treatment are provided in Section 5.6.

5.5 FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event 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's parent or legal guardian withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the subject's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

5.5.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, 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 serious adverse event that occurs after the end of the adverse event reporting period (defined as 6 weeks after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, 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 serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document as "Reference Safety Information":

- Balovaptan Investigator's Brochure

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.

The IMC and the independent SOC will monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Database lock to enable the analysis of the 6-week treatment phase of the study will occur once all subjects have either completed the 6-week assessments or withdrawn from the study early, and all data required for analysis have been cleaned and verified.

The final analysis of all data collected in the study, including the extension period, will occur after all subjects have completed the study.

Details of the planned statistical analyses mentioned below in this section will be fully specified in the Statistical Analysis Plan, which will be finalized prior to the locking the study database.

All subjects who have received at least one dose of the study drug, whether prematurely withdrawn from the study or not, will be included in the safety analysis population. Data will be analyzed according to the expected treatment of 4 mg balovaptan. Any dosing error will be reviewed and the implications of such errors on safety interpretation will be assessed.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size required to determine the dose that will deliver adult-equivalent exposures in pediatric subjects was previously assessed for Study BP30153, based on a bootstrapping methodology combined with PBPK exposure simulations. With a sample size of 10 children, the 90% CI for the apparent CL estimate was 74%–130% of the true apparent CL for the age group of 5- to 7 year old children, indicating that the derived adult-equivalent dose would result in exposures within approximately 30%–40% of the target exposure (Methodology to Guide Pediatric Dose Adjustments and Determine the Sample Size for Early PK Assessment in Adolescents and Children based on PBPK information. Report 1093374, February 2016).

As the variability in apparent CL is expected to be similar in 2- to 4-year old children as in 5- to 17-year olds (PBPK modeling Report 1084465), the same sample size was assumed appropriate.

The primary CL mechanism of balovaptan is metabolism via CYP3A4 (producing M1, M2, and M3) and to a minor extent by means of CYP2D6 (producing M4). In humans, these systems are known to attain adult capacity per gram of liver tissue in the first few years of life as shown by in vitro enzyme expression data as well as based on clinical pharmacokinetics for known substrates (Salem et al. 2014). In children aged 8–17 years, it has been confirmed that no dose adjustment is required in order to achieve similar

exposures as in adults, whereas in children ages 5–7 years, a reduction in CL of approximately 35% was detected. Approximately 10 subjects treated with active drug in the various age groups in Study BP30153 (8–11 years, 12–14 years, and 15–17 years) have shown to be sufficient to determine the dose that provides equivalent exposure as observed in adults treated with 10 mg with adequate precision.

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.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic (including age and sex) and baseline characteristics will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables, as appropriate.

6.4 PHARMACOKINETIC ANALYSES

Individual and mean plasma concentration data per timepoint will be listed for the parent and metabolite and the ratio of metabolite to parent concentration will be derived.

Nonlinear mixed-effects modeling will be used to analyze the sparse sampling dose-concentration-time data collected for balovaptan. A previously developed pop-PK model will be used to analyze the PK data in this study. Population and individual PK parameters will be estimated and $AUC_{\tau,ss}$ derived from the individual PK model parameter estimates. The dose resulting in an adult-equivalent exposure will be calculated from the ratio of apparent CL estimates in 2- to 4- year-old children to apparent CL in adults.

The results of the pop-PK model based analyses may be reported in a document separate from the clinical study report.

Exposure equivalence with adult exposures after QD dosing with age-adjusted 10-mg dose of balovaptan will be confirmed, and if needed, dose-adjustment recommendations will be made for subjects continuing in the extension period.

6.5 SAFETY ANALYSES

All safety data will be reported in individual listings and summarized by assessment time using descriptive statistics. Data collected during the follow-up period (i.e., after discontinuation of study treatment) will be summarized separately from the data collected during the treatment period.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms and adverse event severity will be graded according to Table 3. The incidence of adverse

events will be summarized on the basis of body systems, dictionary-preferred terms by severity and relationship to study drug.

[redacted]

Treatment-emergent abnormalities from physical and neurological examinations will be listed by treatment and subject to statistical analysis where applicable.

6.6 EFFICACY ANALYSES

All exploratory efficacy data from baseline and following visits as well as participants' demographics and baseline characteristics (age, sex, comorbidities, pharmacological and non-pharmacological treatment etc.) will be listed and summarized using descriptive statistics providing means, medians, standard deviations, and range values.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and electronic clinical outcome assessment (eCOA) data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

eCOA data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

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

All eCRFs should be completed by designated, trained site staff. 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 data is required.

7.3 ELECTRONIC CLINICAL OUTCOME DATA

An electronic device will be used to capture eCOA data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR, Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure vendor web portal. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive subject data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 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, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (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 7.6.

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

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO and ObsRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each subject or the subject's legally authorized representative the objectives, methods, and potential risks associated with each optional procedure. Subjects or the subject's legally authorized representative 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 or subject's legally authorized representative's agreement to participate in optional procedures. Subjects or subject's legally authorized representatives 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 or the subject's legally authorized representatives 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.

For sites in the United States, each Consent Form may also include subject or legally authorized representative authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for subject authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the subject, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any subject recruitment materials must be approved by the IRB/EC.

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 10 sites globally will participate to enroll approximately 10 subjects. Enrollment will be managed through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker, and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC and SOC will be employed to monitor and evaluate subject safety throughout the study.

9.5 DISSEMINATION 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, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

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 patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients 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 the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

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

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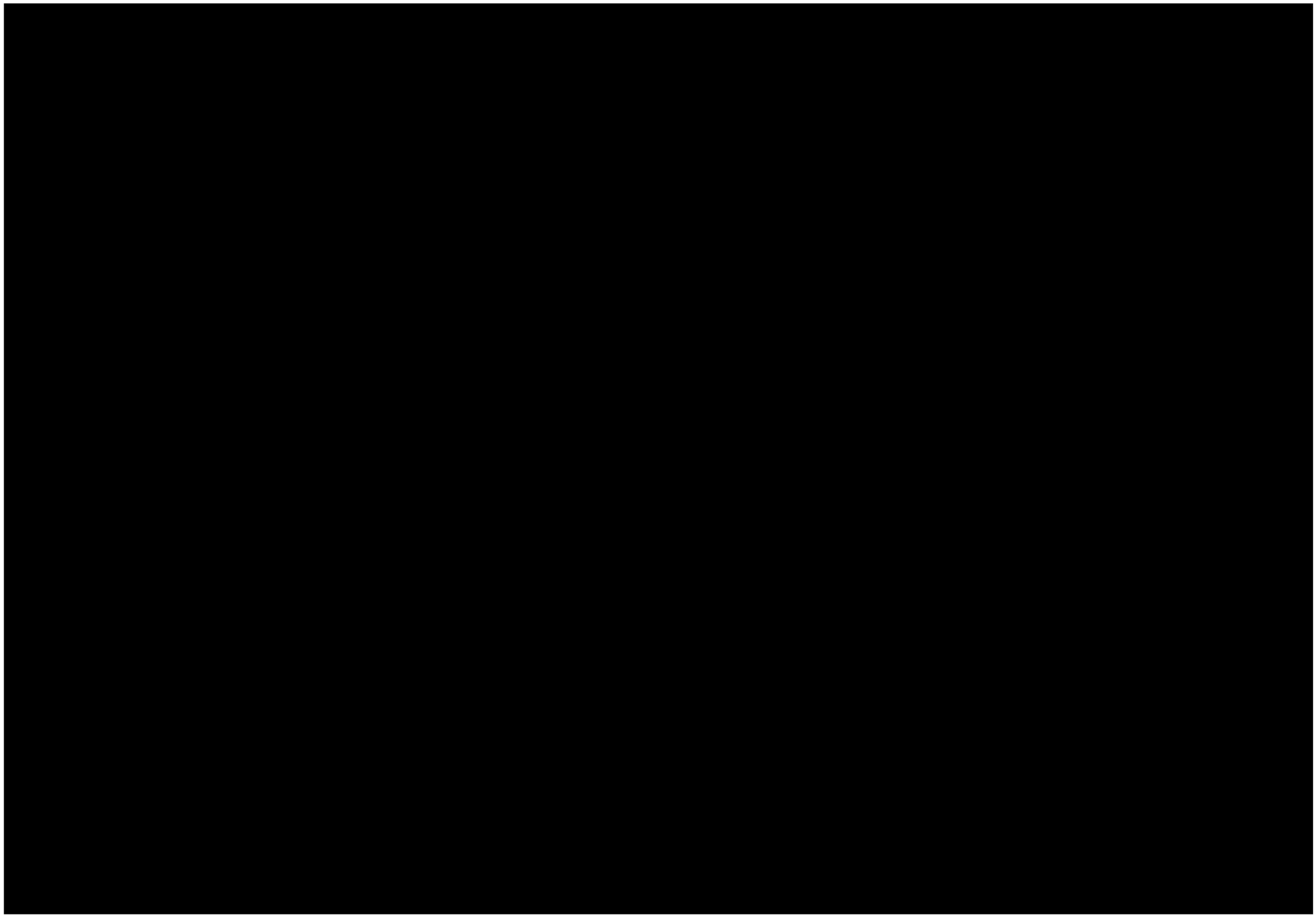

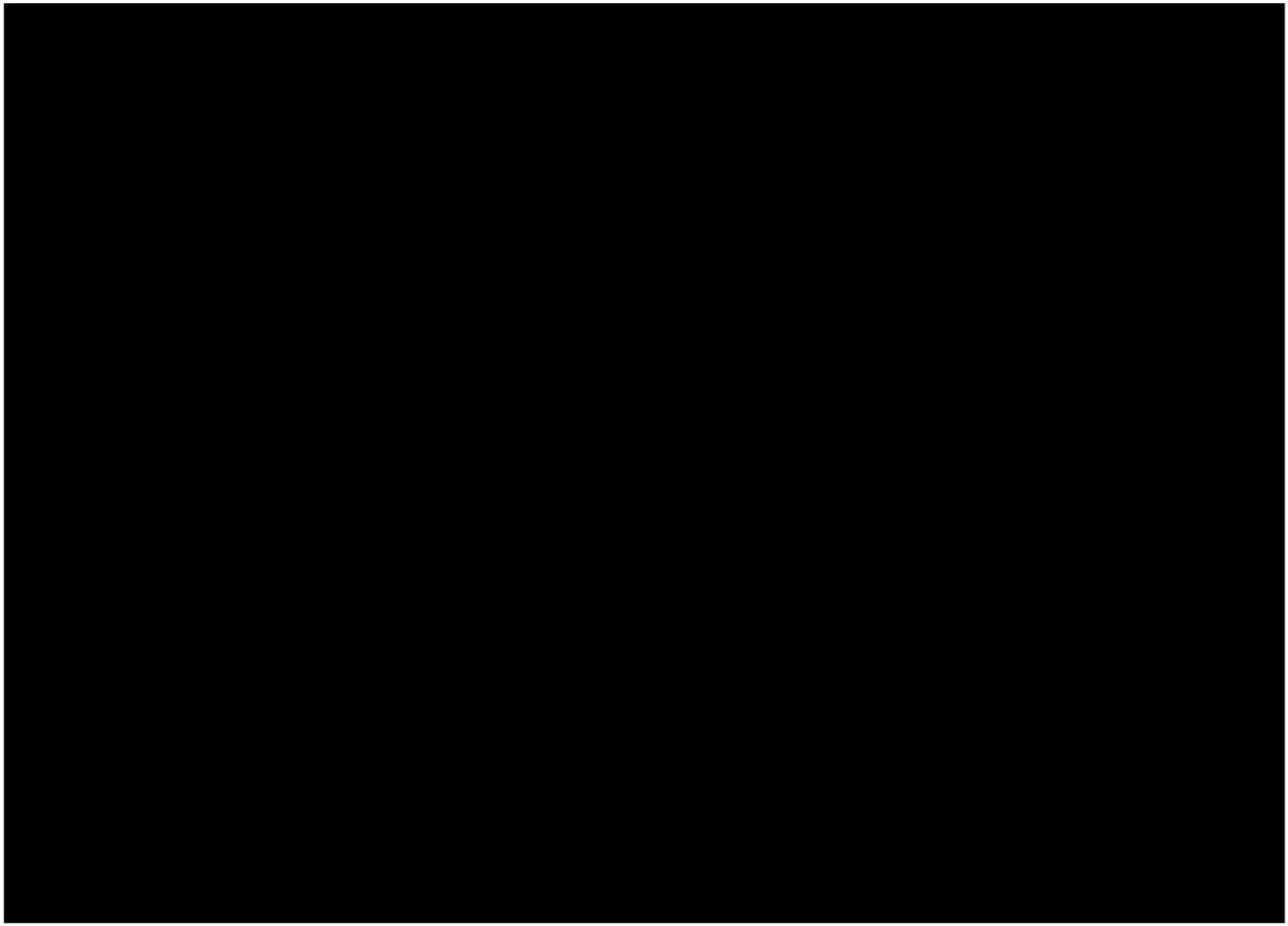

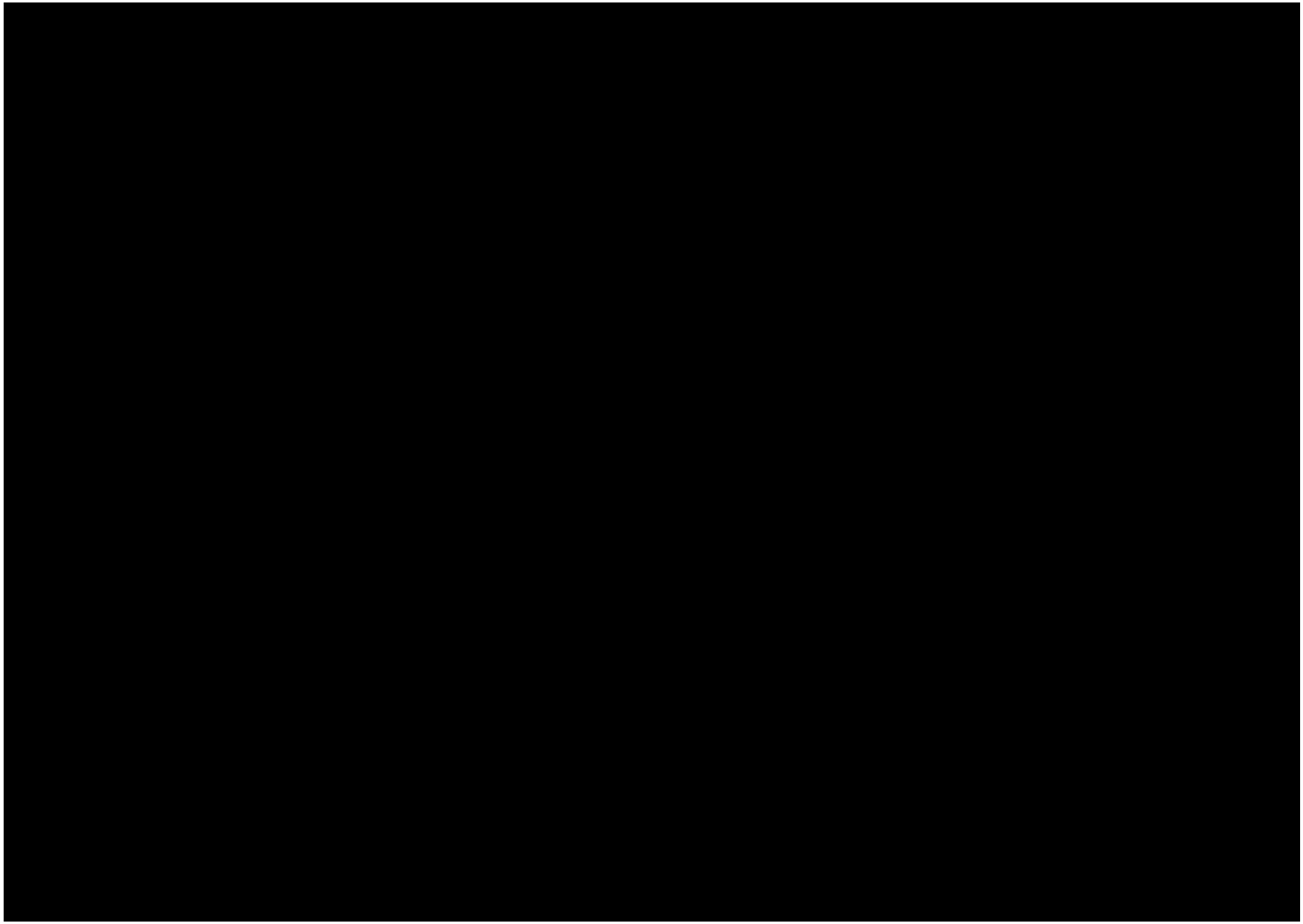

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