Official Title: A Phase II Multicenter, Randomized, Double-Blind, 12-Week Treatment, 3-Arm, Parallel-Group, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of RO7017773 in Participants Aged 15 to 45 Years With Autism Spectrum Disorder (ASD)

NCT Number: NCT04299464

Document Date: Protocol Version 5: 02-June-2022

PROTOCOL

TITLE:	**A PHASE II MULTICENTER, RANDOMIZED, DOUBLE-BLIND, 12-WEEK TREATMENT, 3-ARM, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY, SAFETY AND TOLERABILITY OF RO7017773 IN PARTICIPANTS AGED 15 TO 45 YEARS WITH AUTISM SPECTRUM DISORDER (ASD)**
PROTOCOL NUMBER:	BP41316
VERSION:	5
EUDRACT NUMBER:	2019-003524-20
IND NUMBER:	141893
TEST PRODUCT:	RO7017773
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 23 Nov 2019
DATE AMENDED:	Version 2: 15 May 2020 Version 3: 18 February 2021 Version 4: 25 October 2021 Version 5: See electronic signature and date stamp on the final page of this document

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE II MULTICENTER, RANDOMIZED, DOUBLE-BLIND, 12-WEEK TREATMENT, 3-ARM, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY, SAFETY AND TOLERABILITY OF RO7017773 IN PARTICIPANTS AGED 15 TO 45 YEARS WITH AUTISM SPECTRUM DISORDER (ASD)**
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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 Site Monitor.

PROTOCOL AMENDMENT, VERSION 5
RATIONALE

Protocol BP41316 has been amended to reduce the study burden for participants and their caregivers, reduce the duration of study visits, and provide additional flexibility to schedule study visits and perform specific study assessments remotely. Changes to the protocol, along with a rationale for each change, are summarized below:

- **Changes to reduce the study burden**
  - In Table 1, administration of Pediatric Quality of Life Inventory™ (PedsQL™) Family Impact Module has been removed to reduce study burden for participants and caregivers. Section 3 (Objectives and Endpoints) has been updated accordingly and Section 8.1.5.10 (Pediatric Quality of Life Inventory™ [PedsQL™] Version 2.0 Family Impact Scale) in the previous version of the protocol has been removed.
  - A new table (Table 2 Visit Scheduling Details) has been added to provide more flexibility for participants, to enhance study feasibility, and to reduce burden for caregivers by extending screening period in case of logistic reasons and allowing split visits for any day within visit time windows.
  - To provide more flexibility, footnote d has been added to Table 3 to clarify that completion of in-clinic assessments can be done either at baseline or on Day 1.
  - Sections 1.3 (Schedule of Activities), 3 (Objectives and Endpoints), 4.2.3.2 (Rationale for Response Biomarkers), and 8.7.1.4 (Response Biomarkers: Eye-Tracking and EEG Biomarkers) have been updated to remove part of the electroencephalogram (EEG)/electrooculogram (EOG) assessments in order to reduce the duration of the trial's visits. Auditory EEG tasks have been removed from Pre-Baseline and Week 12 visits, and the saccadic peak velocity (SPV) task has been removed from Week 12.
  - Section 1.3 (Schedule of Activities) and Section 8.7.1.1 (Digital Biomarkers) have been updated to reduce the time that participants and their support person need to spend on the digital biomarker assessments, including the following changes: (1) removal of surveys from the smartphone app, except the EuroQol 5 Dimension 5-Level Questionnaire (EQ-5D-5L); (2) removal of one of the four active tasks from the smartphone app; (3) use of the beacons is optional; and (4) reduction of the frequency of at-home active tests from 7 per week (i.e., once every day) to 3 per week (i.e., all tests once per week).
  - To reduce the burden on support person, Section 4.1 (Study Design), Section 5.1 (inclusion criterion #2), and Appendix 1, Section 2.1.2.2 (Remote Administration of Electronic Clinical Outcome Assessments) have been updated to clarify that for support persons of high-functioning adult participants, no on-site visits are necessary after the screening visit if all electronic clinical outcome assessments (eCOA), interview, and forms are performed remotely.

- To reduce the duration of site visits and increase flexibility for both sites and study participants, Appendix 1, Section 2.1.2.2 (Remote Administration of Electronic Clinical Outcome Assessments) has been updated to clarify that all caregiver- and patient-reported scales, forms, and interviews including the Vineland-3, Children's Yale-Brown Obsessive Compulsive Scale modified for ASD (CY-BOCS-ASD), and Clinical Global Impression (CGI) assessments may be administered remotely at the participants' home.

- **Changes related to pharmacokinetics**
  - Footnote #11 in Table 1 and Section 8.5 (Pharmacokinetics) have been updated following review of the initial pharmacokinetic (PK) data from 13 high-functioning adult participants. In high- and low-functioning adult participants, the PK sampling has been reduced on Day 1. Additionally, in low-functioning adult participants only, the Week 2, 6-hour PK sample is optional. In adolescents, all PK samples on Day 1 still remain mandatory until the 2nd Internal Monitoring Committee (IMC) + Scientific Oversight Committee (SOC) review.
  - Section 8.5. (Pharmacokinetics) and footnote #10 in Table 1 has been updated to ensure that study drug is administered with breakfast/some food on Day 1 and Day 14 to ensure accurate capturing of the peak concentrations of RO7017773 as emerging PK data suggests a t_{max} of approximately 2 hours following a light meal.
  - Footnote #8 in Table 1 has been updated with regards to postdose ECG measurements on Day 1 and Day 14; ECG assessments at 4 hours postdose on these days were removed as the emerging PK data suggests a t_{max} of approximately 2 hours corresponding to highest plasma concentrations for RO7017773 following a light meal. Therefore, ECG assessments will be reduced to one timepoint postdose (2 hours) to capture peak effect on ECG parameters.

- **Changes to eligibility criteria**
  - Section 5.1 (Inclusion Criteria) has been updated to remove the Clinical Global Impression-Severity (CGI-S) scale as an inclusion criterion. This additional criterion is not necessary to select the target study population as both core symptoms are enriched by more specific severity-based inclusion criteria. Section 5.4 (Screen Failures) has also been updated accordingly.
  - Inclusion criterion #8 (Section 5.1 Inclusion Criteria) and Section 8.1.4.1 (Wechsler Abbreviated Scale of Intelligence, Second Edition) have been updated regarding the possibility to use previous intelligence quotient (IQ) assessments for adult participants.
  - Section 5.2 (Exclusion Criteria) has been updated to clarify the eligibility of subjects with syndromic forms of autism spectrum disorder (ASD) and genetic alterations strongly associated with ASD.
  - Sections 5.1 (Inclusion Criteria) and 4.2.1 (Rationale for Study Population) have been updated to lower the inclusion threshold for the CY-BOCS-ASD to a total score of at least 8 on the basis of new data indicating that an inclusion

threshold of 8 is sufficient to recruit a study population with elevated levels of restricted and repetitive behaviors. With this change, the Sponsor aims to avoid exclusion of subjects with sufficiently high levels of restricted and repetitive behaviors that are suitable to monitor these behaviors in the context of this study. Section 5.4 (Screen Failures) has also been updated to clarify that participants who meet the updated inclusion threshold are eligible to re-screening.

- **Other changes**
  - Table 1 has been updated to move the administration of the initial CGI-S clinical interview from screening to pre-baseline. Section 8.1.5.4 and Table 9 have been updated accordingly.
  - It has been clarified that follow-up period will start from the Week 12 visit (Table 1).
  - Footnote #33 in Table 1 has been updated to clarify that the mandatory hair sample will only be collected from participants who have sufficient hair. Section 8.8.1 (Mandatory Samples) has also been updated accordingly.
  - Section 6.5.3 (Prohibited Therapy) has been updated to state explicitly that topiramate, felbamate, zonisamide, and pregabalin are prohibited in this study. Appendix 6 has been updated accordingly.
  - Section 8.1.5.10 (Neurocognitive Battery) and footnote #3 in Table 9 have been updated to clarify that for low-functioning participants, the selection of attention tasks from the neurocognitive battery should be prioritized and performed first.
  - Section 8.7.1.4 (Response Biomarkers: Eye-Tracking and Task EEG Biomarkers) has been updated to clarify that for low-functioning participants, response biomarker assessments may be skipped if they are not able to complete the full set of assessments.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADOS-2	Autism Diagnostic Observation Schedule, Second Edition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
ASD	Autism spectrum disorder
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}inf}$	Area under the concentration–time curve from time 0 to infinity
AUC_{τ}	Area under the concentration-time curve for a dosing interval
BA	Bioavailability
BAI	Beck Anxiety Inventory
BID	Twice a day
BMI	Body mass index
BP	Blood pressure
BRCP	Breast cancer resistance protein
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C_{max}	Maximum concentration
CNS	Central nervous system
COA	Clinical outcome assessments
CPAL	Continuous Paired Associate Learning Test
CRRI	Caregiver-Reported Routines Inventory
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide-Severity Rating Scale
CT	Clinical team
CTCAE	Common Terminology Criteria for Adverse Events
CY-BOCS-ASD	Children's Yale-Brown Obsessive Compulsive Scale modified for Autism Spectrum Disorder
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDAVP	1-deamino-8-D-arginine vasopressin

Abbreviation	Definition
DDI	Drug-drug interaction
DET	Detection Test
DRF	Dose-range finding
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EAF	Eligibility assessment form
EAP	Efficacy Analysis Population
EC	Ethics Committee
EC_{50}	Half maximally effective concentration
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EEA	European Economic Area
EEG	Electroencephalogram
EFD	Embryofetal development
E_{max}	Maximum effect
EOG	Electrooculogram
EQ-5D-5L	EuroQol 5-Dimension 5-Level Questionnaire
ESS	Epworth Sleepiness Scale
ESS-CHAD	Epworth Sleepiness Scale for Children and Adolescents
EU	European Union
FE	Food effect
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
$GABA_A$	Gamma-aminobutyric acid type A
$GABA_A$ α5	Gamma-aminobutyric acid type A, alpha 5
GLDH	Glutamate dehydrogenase
GMLT	Groton Maze Learning Test
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein (cholesterol)
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate

Abbreviation	Definition
HRQoL	Health-related quality of life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Intellectual disability
IDN	Identification Test
IEC	Independent Ethics Committee
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IQ	Intelligence quotient
ISL	International Shopping List Test
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
IxRS	IVRS or IWRS (Interactive voice response system or Interactive web response system)
KSS	Karolinska Sleepiness Scale
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LF	Low functioning participant
LFA	Low-functioning adult
LPLV	Last participant, last visit
MAD	Multiple-ascending dose
NDD	Neurodevelopmental disorder
NGS	Next generation sequencing
NIMP	Non-investigational medicinal product
NSAESI	Non-serious adverse event of special interest
OCL	One Card Learning Test
ONB	One Back Test
OTC	Over-the-counter
PAM	Positive allosteric modulator
PD	Pharmacodynamic
PedsQL™	Pediatric Quality of Life Inventory™
PET	Positron emission tomography
P-gp	P-glycoprotein
phMRI	Pharmacological magnetic resonance imaging

Abbreviation	Definition
PK	Pharmacokinetic
pop-PK	Population pharmacokinetic
PRAS-ASD	Parent-Rated Anxiety for Autism Spectrum Disorder
PRN	As needed
PROMIS	Patient-Reported Outcomes Measurements Information System
PTZ	Pentylenetetrazole
[redacted]	
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTca	QTc individually corrected for heart rate
QTcB	QT corrected for heart rate using the Bazett's correction factor
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	Red blood cell
RBR	Research Biosample Repository
RBS-R	Repetitive Behavior Scale-Revised
RO	Receptor occupancy
RNA	Ribonucleic acid
RRB	Restricted and repetitive behavior
SAD	Single-ascending dose
SAE	Serious adverse event
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SNRI	Serotonin-norepinephrine reuptake inhibitor
SoA	Schedule of Activities
SOC	Scientific Oversight Committee
SPV	Saccadic peak velocity
SRS-2	Social Responsiveness Scale, Second Edition
SSP-2	Short Sensory Profile, Second Edition
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Half-life
t_{max}	Time of maximum concentration observed
TSH	Thyroid-stimulating hormone
TWOB	Two Back Test

Abbreviation	Definition
ULN	Upper limit of normal
Vineland™ II	Vineland™ Adaptive Behavior Scales, Second Edition
Vineland™-3	Vineland™ Adaptive Behavior Scales, Third Edition
V_{ss}	Volume of distribution under steady-state conditions
WAIS	Wechsler Adult Intelligence Scale
WASI-II	Wechsler Abbreviated Scale of Intelligence, Second Edition
WBC	White blood cell
WES	Whole exome sequencing
WGS	Whole genome sequencing
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE II MULTICENTER, RANDOMIZED, DOUBLE-BLIND, 12-WEEK TREATMENT, 3-ARM, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY, SAFETY, AND TOLERABILITY OF RO7017773 IN PARTICPANTS AGED 15 TO 45 YEARS WITH AUTISM SPECTRUM DISORDER (ASD)**
SHORT TITLE	**RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF RO7017773 IN PARTICPANTS AGED 15 TO 45 YEARS WITH AUTISM SPECTRUM DISORDER (ASD)**
PROTOCOL NUMBER:	BP41316
VERSION:	5
TEST PRODUCT:	RO7017773
PHASE:	II

RATIONALE

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by two core domains: impairments in social interaction and communication as well as presence of repetitive or restricted behaviors, interests, or activities. Core symptoms of ASD affecting domains of socialization, communication, and repetitive behavior are usually observed by 3 years of age, although typical language development might delay identification of symptoms. Deficits in socialization manifest themselves as impaired use of non-verbal communication, delayed and reduced interactions with peers, absent sharing of enjoyable experiences and interest with peers, and lack of social judgment. Abnormalities in communication include a delay in verbal language development, impaired expressive language, deficient language pragmatics, as well as stereotyped, repetitive, or idiosyncratic use of language. Stereotyped and repetitive behavior manifests as a preoccupation with stereotyped or restricted interests, adherence to routines, rigidity, perseverative and stereotyped behavior, motor mannerisms, preoccupation, or fascination with parts of items, and unusual visual exploration. In addition to these core deficits, patients with ASD suffer from a range of comorbid conditions, including irritability, depression or anxiety, attention deficits, obsessive compulsive symptoms, seizures, and sleep disruption. RO7017773 is a selective gamma-aminobutyric acid type A, alpha 5 ($GABA_A$-$\alpha5$) subunit-containing receptor positive allosteric modulator (PAM). RO7017773 is being developed for the treatment of the two core domains of ASD: social communication deficits and restricted and repetitive behaviors (RRBs). RO7017773 has the potential to normalize gamma-aminobutyric acid (GABA)-ergic signaling in key brain regions implicated in ASD without the side effects of non-specific GABA modulators (e.g., benzodiazepines).

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 12-week treatment with RO7017773 compared with placebo in treating social communication deficits in participants with ASD	• Change from baseline to Week 12 in the Adaptive Behavior Composite score of the Vineland™ Adaptive Behavior Scales, Third Edition (Vineland™-3)
Secondary	
• To evaluate the safety and tolerability of a 12-week treatment with RO7017773 in 15- to 45-year-old participants with ASD.	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) • Incidence of treatment discontinuations due to AEs • Change from baseline over time and incidence of clinically relevant abnormalities in vital signs including orthostatic changes, electrocardiogram (ECG) parameters and safety laboratory values including the incidence of marked laboratory abnormalities • Change from baseline over time in suicide risk (using the Columbia-Suicide-Severity Rating Scale [C-SSRS]) • Incidence of daytime sleepiness assessed with the Karolinska Sleepiness Scale (KSS), the Epworth Sleepiness Scale (ESS) or the ESS for children and adolescents (ESS-CHAD), and the Sudden Onset of Sleep Questionnaire
• To evaluate the efficacy of a 12-week treatment with RO7017773 compared with placebo on restricted and repetitive behaviors (RRBs)	• Change from baseline to Week 12 in behavior/symptoms as measured by all domains of the Repetitive Behavior Scale-Revised (RBS-R) scale
• To evaluate the efficacy of a 12-week treatment with RO7017773 compared with placebo on social behaviors	• Change from baseline to Week 12 on the Vineland-3 Socialization domain
• To evaluate the efficacy of a 12-week treatment with RO7017773 compared with placebo on communication skills	• Change from baseline to Week 12 on the Vineland-3 Communication domains

OVERALL DESIGN

This is a multicenter, randomized, double-blind, parallel-group, 3-arm, placebo-controlled, 12-week treatment Phase II study to investigate the efficacy, safety and tolerability, and pharmacokinetics of RO7017773 in participants aged 15 to 45 years with a diagnosis of ASD and Wechsler Abbreviated Scale of Intelligence (WASI-II) score ≥50.

STUDY DESIGN

Approximately 105 participants with ASD (in order to have approximately 84 evaluable participants at study end) aged 15 to 45 years will be enrolled into the study. Participants will be

randomized [redacted] in a 1:1:1 ratio (35 participants randomized to each treatment arm).

After approximately 18 high-functioning (WASI-II ≥70) adults (aged 18 to 45 years) have completed 6 weeks of treatment [redacted] the Internal Monitoring Committee (IMC) with the Scientific Oversight Committee (SOC) will conduct a pharmacokinetic (PK), safety, and tolerability review. Once adequate PK, safety, and tolerability in high-functioning adults have been established and PK-model predictions from healthy adult volunteers are confirmed to be comparable with the PK results in high-functioning adults, then low-functioning adults (WASI ≥ 50 to 69) and adolescents aged 15 to 17 years (both high- and low-functioning) will be included into the study. A second IMC + SOC review will be performed to evaluate PK, safety, and tolerability data from all available participants once at least 12 adolescents have completed 2 weeks of treatment.

Randomization will take place on Day 1 after a screening period of at least 2 to up to 4 weeks and after a pre-baseline and a baseline visit as indicated in the SoA. Randomization to the different treatment arms will be stratified by age and intelligence quotient (IQ).

Each participant will be evaluated using several scales and tests at each visit at the clinic. A total of 9 clinic visits (screening period included) and 1 phone contact, to assess for any clinically significant symptoms and/or new medication, are planned. In addition, digital biomarker data will be collected from all participants.

Each participant will need a reliable caregiver, parent, or support person who will oversee the participant's adherence with protocol-specified procedures and provide feedback on all informant- based assessments throughout the study. The same support person must attend all on-site visits. *For support persons of high-functioning adult participants, no on-site visits are necessary after the screening visit if the support persons opt to complete all electronic clinical outcome assessments (eCOA), interview, and forms remotely.*

TREATMENT GROUPS AND DURATION

[redacted]

The investigational medicinal products (IMPs) are RO7017773, [redacted] tablets, and matching placebo of RO7017773.

LENGTH OF STUDY

The total duration of the study for each participant will be up to 24 weeks (approximately 5.6 months), divided as follows:

- Screening period of at least 2 and up to 4 weeks
- Study pre-baseline and baseline period (2 weeks)
- Study treatment period with fixed dose (12 weeks)
- Safety and efficacy follow-up period (6 weeks).

END OF STUDY

A participant is considered to have completed the study if he/she has completed the last scheduled procedure.

The end of the study will be considered to be the date of the last visit (including the last follow-up visit) of the last participant in the study (last participant, last visit [LPLV]).

INTERNAL MONITORING COMMITTEE (IMC) AND SCIENTIFIC OVERSIGHT COMMITTEE (SOC)

An IMC consisting of a selected subset of Roche representative(s) will be responsible to perform interim analyses of accumulated safety, tolerability, PK, and efficacy (as required) data. The IMC members, the clinical pharmacologist, and the pharmacometrician will be unblinded to individual study treatment allocation. An SOC consisting of at least one external expert will support the IMC in making their recommendations. These SOC members will likewise be unblinded to individual study treatment allocation.

Access to treatment assignment information will follow the Sponsor's standard procedures.

PARTICIPANT POPULATION

Male and female participants aged 15 to 45 years with ASD according to the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) criteria who fulfill all the inclusion criteria listed below and for whom none of the exclusion criteria listed below apply will be included into the study.

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Study participants or legal representatives should be able and willing to provide written informed consent or assent, as applicable and as per local requirements according to International Council for Harmonisation (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the participant according to ICH and local regulations and assent must be given whenever possible. The ability to provide informed consent for each participant will be based on the Principal investigator's clinical judgment.
2. Availability of a parent or other reliable support person who is fluent in local language and has frequent and sufficient contact with the participant. The same person must agree to accompany the participant to all clinic visits and provide information about the participant's behavior and symptoms and must agree to oversee the participant's adherence with protocol-specified procedures and study medication dosing.
    - *For support persons of high-functioning adult participants, no on-site visits are necessary after the screening visit if all eCOA assessments, interview, and forms are performed remotely.*

Age

3. Age 15 to 45 years, at the time of signing the informed consent or assent form

Type of Participants and Disease Characteristics

4. Male and female participants with Autism Spectrum Disorder (ASD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.
    - For transgender participants, the Investigator should consult with the Medical Monitor or delegate to assess potential safety concerns or interference with safety and efficacy testing. Transgender participants will be enrolled by their biological sex.

    Note: It is important that a high-confidence autism diagnosis has been established by an autism expert prior to screening and is supported by medical records.
5. Social Responsiveness Scale, Second Edition (SRS-2) (T-score) ≥ 66.
6. Wechsler Abbreviated Scale Intelligence second edition (WASI-II) or equivalent assessment ≥ 50 at screening or within the last 12 months prior to screening *(for adults within the last 5 years prior to screening if the assessment was done at age 18 or older)*. The proportion of low-functioning participants (IQ ≥ 50 to 69) will be limited to 25% overall.
    - If a previous assessment is used, the Investigator should assess whether it has been performed by an appropriately qualified rater.
7. ASD or autism diagnosis confirmed by Autism Diagnostic Observation Schedule (ADOS-2), done by a certified rater at screening, or within the last 6 months prior to screening.
8. Presence of at least moderate to severe repetitive behaviors as per Children's Yale-Brown Obsessive Compulsive Scale modified for ASD (CY-BOCS-ASD) total score of at least *8* at screening.

Weight

9. Body mass index (BMI) within the range of 18.5 to 40 kg/m^2 (inclusive).

Sex

10. Male and female participants with contraception requirements.

The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

a) Female Participants

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Women of non-childbearing potential (WONCBP) as defined in Appendix 5
- Women of childbearing potential (WOCBP), who:

– Agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods (hormonal or non-hormonal) that result in a failure rate of <1% per year during the treatment period and for at least 28 days after the last dose of study drug. Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices (see Appendix 5).

Hormonal contraceptive methods must be supplemented by a barrier method (as defined in Appendix 5, preferably a condom with a spermicide) if participants are receiving any drug known to reduce the effect of hormonal contraception (including anti-epileptic drugs inducing drug metabolism). In such a situation, the risk assessment should be discussed with the Medical Monitor.

Note: Females who reach menarche after enrollment in the study must agree from this time forward to regular blood or urine pregnancy testing as defined in the Schedule of Activities (SoA) and must agree to either remain completely sexually abstinent or comply with the same contraceptive requirements as outlined above for WOCBP from first menses until 28 days after the last dose of study treatment (see Appendix 5).

b) Male Participants

Male contraception is not required in this study because of the minimal seminal dose transmitted through sexual intercourse (Banholzer et al 2016, Appendix 5).

Additional Inclusion Criteria:

11. Language, hearing, and vision compatible with the study measurements as judged by the Investigator. Non-verbal individuals will be excluded from study participation.
12. Allowed existing treatment regimens should be stable for 8 weeks prior to screening except:
    - 6 weeks for non-pharmacological interventions
    - 12 weeks in the case of antipsychotic therapies
    - 6 months for antiepileptic treatments

    Investigator expects stability of these treatments and behavioral interventions for the duration of the study.
13. In the Investigator's opinion, able to participate and deemed appropriate for participation in the study, capable of following the study SoA and able to comply with the study restrictions.
14. In the Investigator's opinion, participation in the study or discontinuation of prohibited medication will not pose undue risks.

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

Neurologic/psychiatric conditions

1. Presence of chromosome 15q11.2 q13.1 duplication syndrome (Dup15q syndrome), known "syndromic" forms of ASD *(confirmed per genetic results available at screening):* fragile X syndrome, Prader Willi syndrome, Rett's syndrome, tuberous sclerosis, *and Angelman syndrome, as well as genetic alterations strongly associated with ASD per genetic results available at screening affecting the following genes: CHD8, ANDP, SHANK3.*
    - Clinical suspicion of the presence of Dup15q syndrome should lead to study exclusion. Please contact the Medical Monitor for any questions related to a clinical suspicion of Dup15q syndrome.
    - *Other genetic information available at screening should be taken into consideration for assessment of participant eligibility. The Principal Investigators are encouraged to consult with the Sponsor (Medical Monitor or designee) for advice.*
2. Medical history of alcohol and/or substance abuse/dependence in the last 12 months or positive test for drugs of abuse at screening (unless the finding is related to the intake of concomitant medications allowed by the protocol).
3. Initiation of a major change in psychosocial intervention (including investigational) within 6 weeks prior to screening. Minor changes in ongoing treatment (e.g., missed therapy sessions due to holiday/vacation; planned break in therapy due to holidays; changes in college/university programs) are not considered major changes.
4. Clinically significant psychiatric and/or neurological disorder that may interfere with the safety or efficacy endpoints.
    - Participants with a psychiatric diagnosis other than ASD, including but not limited to, bipolar disorder, psychosis, schizophrenia, post-traumatic stress disorder or major depressive disorder will be excluded if the psychiatric comorbidity has the potential to confound results or impact safety.
    - Participants with non-suicidal self-injurious behaviors (e.g., cutting, head banging) that interferes with safety and efficacy testing will be excluded.
5. Risk of suicidal behavior in the opinion of a certified clinician or as evidenced by a "yes" to questions 4 and/or 5 of Columbia-Suicide-Severity Rating Scale (C-SSRS) taken at screening with respect to the last 12 months or any suicide attempt in the past 5 years.
6. Unstable epilepsy/seizure disorder within the past 6 months.

Cardiovascular conditions

7. Concurrent cardiovascular disease considered not well controlled by drug treatment, including participants with clinically significant hypertension, bradycardia and arrhythmias, myocardial infarction within 12 months of screening or uncompensated heart failure.
8. Confirmed clinically significant abnormality on 12-lead electrocardiogram (ECG), including a QTc of ≥450 ms (based on the average of 3 consecutive measurements). Central ECG readings should be used to determine if this criterion is met.
9. Congenital heart diseases not treated and congenital QTc prolongation or family history of Long QT Syndrome.

Other conditions

10. Medical history of malignancy if not considered cured or if occurred within the last 3 years with the exception of fully excised non-melanoma skin cancers or in-situ carcinoma of the cervix that has been successfully treated.
11. Concomitant disease, condition, or treatment which would either interfere with the conduct of the study or pose an unacceptable risk to the participant in the opinion of the Investigator.
12. Known active or uncontrolled bacterial, viral, or other infection (excluding fungal infections of nail beds) or any major episode of infection or hospitalization (relating to the completion of the course of antibiotics) within 6 weeks prior to the start of drug administration.

Prior/Concomitant Therapy

13. Use of prohibited medications or herbal remedies (with the exception of herbal remedies approved by the Medical Monitor or designee) within 6 weeks or 5 half-lives (t1/2) prior to randomization, (whichever is longer).

Prior/Concurrent Clinical Study Experience

14. Donation or loss of blood over 500 mL in adults and 250 mL in adolescents within 3 months prior to randomization.
15. Participation in an investigational drug study within 1 month or 5 times the $t_{1/2}$ of the investigational molecule (whichever is longer) prior to randomization or participation in a study testing an investigational medical device within 1 month prior to randomization or if the device is still active.
16. Sensitivity to any of the study treatments or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study.

Diagnostic Assessments

17. Confirmed clinically significant abnormality in hematological, chemistry or coagulation laboratory parameters.
18. Positive test result at screening for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV, untreated), or human immunodeficiency virus (HIV)-1/2. HCV participants who have been successfully treated and who test negative for HCV RNA may be considered eligible for entry into the study.

Other Exclusions

19. Uncorrected hypokalemia or hypomagnesaemia.

NUMBER OF PARTICIPANTS

Approximately 105 participants with ASD randomized in a 1:1:1 ratio between two active dosing regimens and placebo need to be recruited in order to obtain evaluable data from at least 84 participants after 12 weeks of treatment.

CONCOMITANT THERAPY

Permitted Therapy

Participants must be on a stable prescribed medication regimen for 8 weeks before screening, with the exception of antipsychotic therapies and antiepileptic treatments (where participants need to be on a stable regimen for at least 12 weeks and 6 months before screening, respectively; see inclusion criterion *12*). Any stable prescribed medication at screening should remain stable throughout the study. All changes in prescribed medication need to be discussed with the Sponsor (Medical Monitor or designee).

Examples of allowed medications:

Use of the following therapies is permitted, as specified below:

- Selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRI/SNRI) antidepressants including fluoxetine (see also inclusion criteria)

- Melatonin
- Trazodone (at low doses) for insomnia
- Aripiprazole
- Risperidone
- Psychostimulants (e.g., methylphenidate)
- Clonidine
- Occasional use of paracetamol/acetaminophen
- Antiepileptic medication (carbamazepine and phenytoin are prohibited because of cytochrome P450 [CYP] 3A4 induction) must be stable for 6 months
- Benzodiazepines with a short $t_{1/2}$ (e.g., lorazepam, alprazolam, or oxazepam) are allowed if
  - taken only on an as needed (PRN) basis,
  - limited to 3 times per week,
  - prescribed for short-term or intermittent medical conditions and,
  - not taken immediately before the assessments visits (i.e., not within 2 days or within 5 times the elimination t1/2, whichever is longer before a scheduled visit).

  Note: for benzodiazepines with a long $t_{1/2}$ (except for benzodiazepines to treat emerging symptoms of rebound and/or withdrawal effects) see below (Prohibited Therapy).
- Drugs known to prolong the QTc interval will be allowed if stable at screening provided the screening QTc does not meets exclusion QTc criterion (see list of drugs known to prolong QT in Appendix 8 of the protocol).
- Any medication for medical illnesses other than ASD not listed under prohibited medications
- Vaccines, including those against COVID-19

Any other medications require the approval from the Investigator and the Sponsor's Medical Monitor (or designee).

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

PROHIBITED THERAPY

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, oral contraceptives, hormone-replacement therapy, or other maintenance therapy listed above unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Use of the following therapies (e.g., prescription drugs, over-the-counter (OTC) drugs, herbal remedies, nutritional supplements) is prohibited during the study and for at least 6 weeks prior to randomization (or within 5 times the elimination $t_{1/2}$, whichever is longer) to ensure washout of medication and until follow-up, unless otherwise specified below.

<u>Examples of prohibited medications:</u>

- Strong inhibitors of CYP3A4/5 (e.g., ketoconazole, clarithromycin, grapefruit juice)
- Strong inducers of CYP3A4 (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's Wort)
- Under no circumstances should a strong CYP3A4 inhibitor be given in combination because of the potential increase in exposure. If the use of a strong inhibitor is indicated, the Investigator should contact the Sponsor to discuss alternative options (e.g., replacement of clarithromycin by azithromycin, which is not a CYP3A4 inhibitor). For certain cases, the Sponsor may advise pausing the treatment with RO7017773 and restarting when the CYP3A4 inhibitor has been discontinued and 5 times the elimination $t_{1/2}$ of the CYP3A4 inhibitor have elapsed.
- Chronic adrenocorticoid or glucocorticoid use (use of inhaled and topical formulations are allowed)

- *Regarding the use of* anxiolytics, sedative, and hypnotics: benzodiazepines with a long $t_{1/2}$ or benzodiazepine-like drugs pharmacologically similar to benzodiazepine (e.g., zolpidem, zopiclone, eszopiclone, and zaleplon) will not be allowed during screening and treatment periods (for benzodiazepines with a short $t_{1/2}$ that are allowed see above (Permitted Therapy).

  In case of emerging symptoms of rebound and/or withdrawal effects of the study drug during the follow-up period after end of treatment at Week 12, treatment with benzodiazepines is allowed and must be reported on the appropriate section of the electronic case report form (eCRF).
- Barbiturates and opioids
- Alcohol consumption – more than 1 drink per week
- Other GABA agonists (direct/indirect): tiagabine, vigabatrin, baclofen, phenelzine, *topiramate, felbamate, zonisamide, pregabalin*
- Valproic acid and its salts
- Oxytocin
- Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP])
- All other psychotropic medications or medications used for a psychotropic effect (unless allowed by the Medical Monitor or designee)
- Tetrahydrocannabinol due to its psychoactive effects (e.g., marijuana)
- Herbal therapies and dietary supplements including cannabidiol (unless allowed by the Medical Monitor or designee)
- Non-pharmacological interventions cannot be initiated after randomization (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy).

The above list of medications is not exhaustive. The Investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with the study drug. In addition, the Investigator should contact the Medical Monitor or designee if questions arise regarding medications not listed above.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1.

[redacted]

1.3 SCHEDULE OF ACTIVITIES

The Schedule of Activities *(SoA)* is provided in Table 1 *(main SoA)*, *Table 2 (visit scheduling details)*, *Table 3 (SoA for digital biomarkers)*, *and Table 4 (schedule of use of technology for digital biomarkers)*.

Table 1 Schedule of Activities - 12-Week, Double-Blind, Placebo-Controlled Period and Follow-Up

Week	Screening	Pre-Baseline	Baseline	Week 1	Week 1	Week 2	Week 6	Week 12	Follow-up (2 Weeks)	Follow-up (6 Weeks)	Early Termination [3]
Day	D-42 to D-15	Day -14	(Days -3 to -1)	Day 1	Day 7	Day 14	Day 42	Day 84	Week 12 visit + 14 days	Week 12 visit + 42 days	
Visit Window [1]		+/- 3 days			+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	
Assessments	Site Visit	Site Visit	Site Visit	Site Visit	Phone call [20]	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit
Informed Consent [32]	X										
Inclusion/Exclusion criteria	X										
Eligibility Assessment Form (EAF)	X										
Support person instructions	X		X					X			
Pregnancy Test [4]	X		X				X	X		X	X
Demography	X										
Medical History (incl. psychiatry)	X										
Previous and Concomitant Treatments / Medications	X		X	X[9]	X	X	X	X	X	X	X
Physical Examination	X							X		X	X
Anthropometric Measurements [7]	X							X			X
Vital Signs [6]	X			X[6]		X[6]	X[6]	X[6]	X	X	X
Orthostatic changes [6]				X[6]		X[6]	X[6]	X[6]	X	X	X
Triplicate 12-lead ECGs	X			X[8]		X[8]		X[9]	X		X
WASI-II [22]	X										
ADOS-2 [22]	X										
SRS-2 [22]	X										
CYBOCS- ASD [22]	X										
Vineland-3 [22]		X	X					X			
RBS-R [22]		X	X					X			
CRRI [30]		X	X					X			
CGI-S [22]		X	X			X	X	X	X	X	X
CGI-I [22]						X	X	X	X	X	X
BAI [22]			X					X			
PRAS-ASD [22]			X					X			
AASP / SSP-2 [22]			X					X			
Peds-QL [22]			X					X			
Neurocognitive full battery [22, 23]		X[5]		X[9]		X[9]	X[9]	X[9]	X	X	X
Neurocognitive battery attention tasks (DET, IDN, ONB) [24]				X		X	X	X			

Table 1 Schedule of Activities - 12-Week, Double-Blind, Placebo-Controlled Period and Follow-Up (cont.)

Week	Screening	Pre-Baseline	Baseline	Week 1	Week 1	Week 2	Week 6	Week 12	Follow-up (2 Weeks)	Follow-up (6 Weeks)	Early Termination [3]
Day	D-42 to D-15	Day -14	(Days -3 to -1)	Day 1	Day 7	Day 14	Day 42	Day 84	Week 12 visit + 14 days	Week 12 visit + 42 days	
Visit Window [1]		+/- 3 days			+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	
Assessments	Site Visit	Site Visit	Site Visit	Site Visit	Phone call [20]	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit
KSS [25]				X		X	X	X			
ESS or ESS-CHAD [22]				X		X	X	X			X
Sudden Onset of Sleep Questionnaire				X[2]	X	X	X	X			X
PROMIS Sleep Disturbance Short Form [22]			X					X			
PROMIS Sleep-Related Impairment Short Form [22]			X					X			
PD Biomarker (qEEG, SPV)		X[12]		X[12,14]		X[12]		X[12]			
Response BM (Eyetracking)		X[13]						X[13]			
Response BM (EEG Tasks)		X[13]						X[13]			
Serology [26]	X										
Hematology	X		X			X	X	X	X		X
Blood Chemistry	X[27, 28]		X			X	X[28]	X	X[28]		X
Coagulation	X		X					X	X		X
Urinalysis	X		X			X	X	X	X		X
Drug of abuse/Alcohol test	X		X					X			
Hair sample collection [33]			X				X	X		X	
C-SSRS [31]	X		X			X	X	X	X	X	X
Randomization				X							
Dispensing of study medication				X			X				
Return of study medication							X	X			X
Administration of study medication at clinic [10]											
Digital biomarkers		X[15]									X[15]
PK Sample				X[11,17]		X[11,17]	X[9,17]	X[9,17]			X[17]
Blood sample for Clinical Genotyping								X[16]			
Entry and exit questions [22]			X					X			X
RBR - Optional Whole Blood Sample				X[19]				X[19]			X[19]
Safety serum sample								X[21]			
Adverse Events		X									

Table 1 Schedule of Activities - 12-Week, Double-Blind, Placebo-Controlled Period and Follow-Up (cont.)

ADOS-2 = Autism Diagnostic Observation Schedule, Second Edition; BAI = Beck Anxiety Inventory; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale, CRRI = Caregiver-Reported Routines Inventory; C-SSRS = Columbia-Suicide-Severity Rating Scale; CY-BOCS-ASD = Children's Yale-Brown Obsessive Compulsive Scale Modified for ASD; DET = detection test; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; EEG = electroencephalogram; ESS = Epworth Sleepiness Scale; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents; KSS = Karolinska Sleepiness Scale; GLDH = glutamate dehydrogenase; IDN = identification test; ONB = one back test; PedsQL = Pediatric Quality of Live Inventory; PRAS-ASD = Parent-rated Anxiety Scale for ASD; PROMIS = Patient-Reported Outcomes Measurements Information System; RBR = research biosample repository; RBS-R = Repetitive Behavior Scale-Revised; SARS-Cov-2 = severe acute respiratory syndrome coronavirus 2; SoA = schedule of activities; SPV = saccadic peak velocity; SRS-2 = Social Responsiveness Scale, Second Edition; SSP-2 = Short Sensory Profile-2; Vineland-3 = Vineland Adaptive Behavior Scales, Third Edition; WASI-II = Wechsler Abbreviated Scale of Intelligence, Second Edition.

1 *See Table 2 for details on visit windows and options for remote eCOA administration.*

2 *Sudden onset of sleep questionnaire should be done prior to the study drug administration on Day 1.*

3 If participant discontinues or withdraws from the study treatment prematurely all efforts should be done to perform and complete the Early Termination visit.

4 Blood pregnancy beta-hCG test for women of childbearing potential at screening. At specified subsequent visits, pregnancy test using urine sample will be used. If the participant receives a negative result on urine test, dosing will be carried out. If the participant receives a positive result on urine test, a confirmation with blood test has to be obtained. Both serum and urine pregnancy tests will be analyzed locally at the study sites and not by the central laboratory.

5 Two test sessions of the neurocognitive battery will take place at the pre-baseline visit (see Section 8.1.5.10).

6 For details regarding orthostatic changes, see Section 8.2.3. At visits with dosing, vital signs and orthostatic changes will be measured pre-dose and postdose (hourly for 3 hours [approximately +/- 0.5 hours]), or more frequently if clinically warranted in case of an adverse event of somnolence or sudden onset of sleep.

7 Height and weight will be recorded. For adults, only weight will be measured at Week 12 or Early Termination visit.

8 Predose and at 2 hours (+/- 0.5 hours) postdose on Day 1 and Day 14. All ECGs (12-lead) will be performed in triplicate, 1-2 minutes apart within 5 minutes.

9 Predose

10 [redacted]

Table 1 Schedule of Activities - 12-Week, Double-Blind, Placebo-Controlled Period and Follow-Up (cont.)

11 **Day 1**: 2 hours (+/- 0.5 hours), 4 hours (+/- 0.5 hours), and 6 hours (+0.5 hours) postdose, all on the same day; the last sample can be done on site or at home. *All Day 1 samples are mandatory for adolescents until the 2nd Internal Monitoring Committee (IMC) + Scientific Oversight Committee (SOC) review. Day 1: only 2 hours (+/- 0.5 hours) postdose is mandatory for high- and low-functioning adult participants.*
Day 14: Predose and at 2 hours (+/- 0.5 hours), 4 hours (end of visit but at least 4 hours postdose), and 6 hours (6-8 hours) postdose; the last sample can be done on site or at home, either on the same day or at a later day within the same timeframe. *Day 14: 6 hours (6-8 hours) postdose sample is optional for low-functioning adult participants.*
PK and safety samples will preferably be taken at the site; however, home nursing services will be available to allow for flexibility in the schedule of visits and to shorten site visits when the visit length depends on blood sampling.

12 PD biomarker assessments at time of the day +/- 1 hour of the t_{max} (i.e., approximately 3 to 4 hours postdose *[time window: 2.5 to 4.5 hours postdose]*) at *Pre-Baseline*, Day 1, Week 2 and Week 12 visits *(for resting state qEEG) and at Pre-baseline, Day 1, and Week 2 visits for saccadic peak velocity [SPV], measured by means of electrooculography [EOG] (SPV is not to be assessed at Week 12).*
At pre-baseline visit (no dosing), these assessments should be conducted at about the same time of the day (+/- 1 hour) corresponding to t_{max}, (i.e., approximately 3 to 4 hours postdose at dosing days); The duration is approximately ~15 min assessment time + 30 minutes of EEG preparation time.

13 Eye-tracking and EEG tasks to take place at the time of the day +/-1h of the t_{max} (i.e., approximately 3 to 4 hours postdose *[time window: 2.5 to 4.5 hours postdose]*) at Week 12. At pre-baseline visit (no dosing), these assessments should be conducted at about the same time of the day (+/- 1h) corresponding to t_{max}, (i.e., approximately 3 to 4 hours postdose at dosing days). The duration is approximately *50* min assessment time. The tasks will be performed immediately after the PD Biomarker assessments (see footnote 12) using the same equipment and therefore no extra EEG preparation time is needed.

14 Additional pretreatment PD biomarker assessment on Day 1 (schedule as described in footnote 12). It is not necessary to remove the EEG electrodes after the pretreatment assessment and therefore the EEG preparation time for the 2nd assessment around $t_{max,}$ (i.e., approximately 3-4 hours postdose; see Footnote 12) will be considerably shorter.

15 See Table 3 for details on the digital biomarker SoA.

16 Clinical genotyping sample to be drawn once from every participant at any convenient time between Day 1 and the last visit. Leftover from mandatory genotyping samples will be used for RBR if participant consents to RBR.

17 Leftover from mandatory PK plasma samples will be used for RBR if participant consents to RBR.

19 Whole blood sample will be taken if participant consents to RBR on Day 1 predose and at Week 12 or Early Termination visit.

20 Telephone interview to assess for any clinically significant symptoms and/or new medication.

21 The serum safety sample can be collected any time for specific assay (e.g., GLDH in case of Liver enzymes) if deemed appropriate by the Investigator for the safety evaluation.

22 Refer to Table 9 for further details on the applicable versions of scales to be used according to the age cohort.

Table 1 Schedule of Activities - 12-Week, Double-Blind, Placebo-Controlled Period and Follow-Up (cont.)

23 One of the tests in the neurocognitive battery (International Shopping List [ISL] Test 24h delayed condition) will be performed at 24 hours after the initial tests; it will be conducted at the site if the visit is split into 2 days (see *Table 2*) or over the phone if the participant returned home after the first day. Whenever possible the same test supervisor should perform the initial test and call the participant approximately 24 hours later. Additional questions on duration and quality of sleep will be asked.

24 At visits with dosing, the attention tasks of the neurocognitive battery (DET, IDN, and ONB) will be repeated 3-4 hours post dose.

25 At visits with dosing, the KSS will be done pre-dose and 3-4 hours post dose.

26 At the discretion of the Investigator and Sponsor, participants could be tested for SARS-CoV-2 at screening and at any time during the study.

27 Blood chemistry at screening includes estradiol and FSH (both for female participants only).

28 TSH, free T4, and HbA1c will be assessed at screening, Week 6, and at the 2-week follow-up.

30 Correct version will be predefined on eCOA device: "At baseline" version to be used at pre-baseline and baseline visits; "Since Last Visit" version to be used subsequently.

31 Correct version will be predefined on eCOA device: "At baseline" version to be used at screening visit; "Since Last Visit" version to be used subsequently.

32 The ability to provide informed consent will be evaluated for each participant by the Principal Investigator using their clinical judgment.

33 Hair samples are collected from the study participants *who have sufficient hair only (assessed at each collection timepoint)*. In addition, optional hair samples are collected from the support persons (if consent is given in the applicable Informed Consent Form). All hair strands should be at least 1 cm long.

Table 2 Visit Scheduling Details

Week	*Screening*	*Pre-Baseline*	*Baseline*	*Week 1*	*Week 1*	*Week 2*	*Week 6*	*Week 12*	*Follow-up (2 Weeks)*	*Follow-up (6 Weeks)*	*Early Termination*
Day	*D-42 to D-15*	*Day -14*	*Days -3 to -1*	*Day 1*	*Day 7*	*Day 14*	*Day 42*	*Day 84*	*Week 12 visit + 14 days*	*Week 12 visit + 42 days*	
Visit Window		*+/- 3 days*			*+/- 3 days*	*+/- 7 days*	*+/- 7 days*	*+/- 7 days*	*+/- 7 days*	*+/- 7 days*	*8-day window*
On-site assessments	*May be split up into two visits within a 7-day window (but up to a 15-day window in case of unexpected delays due to logistical or technical reasons).*	*May be split into two visits within visit time window.*	*May be split into two visits within visit time window.*	*Visit cannot be split.*	*N/A*	*Visit cannot be split.*	*May be split into two visits within visit time window.*	*May be split into two consecutive days.*	*May be split into two visits within visit time window.*	*May be split into two visits within visit time window.*	*May be split into two visits within visit time window.*
Remote eCOA assessments	*May be done at any day within visit time window.*	*May be done at any day within visit time window.*	*May be done at any day within visit time window.*			*May be done at any day within visit time window.*	*May be done at any day within visit time window.*	*May be done on any day prior to the last on-site assessment within the visit window*	*May be done at any day within visit time window.*	*May be done at any day within visit time window.*	*May be done at any day within visit time window.*

Table 3 Digital Biomarker Schedule of Activities

	Screening	Pre-baseline	Baseline	Week 1	Week 1	Week 2	Week 6	Week 12	Follow Up (2 Weeks)	Follow Up (6 Weeks)	Early Termination[a]
Day	D-42 to D-15	D-14	D-3 to D-1	Day 1	Day 7	Day 14	Day 42	Day 84	*Week 12 visit +14 days*	*Week 12 visit +42 days*	
Visit window		+/- 3 days			+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	
Assessments	Site Visit	Site Visit	Site Visit	Site Visit	Phone Call	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit
Identification of targeted behaviors for app		X									
Hand over technology and training		X									
Completion of In-Clinic Assessments		X	X[d]			X	X	X			
Completion of At-Home Assessments[e]		*X*									
Review of compliance[b]				X	X	X	X				
Return of technology and completion of satisfaction survey[c]								X			X

a. If participant discontinues or withdraws from the study treatment prematurely all efforts should be done to perform and complete the Early Termination visit.
b. Participants with inadequate compliance will be re-encouraged to use the digital biomarker technology. If technical problems are identified devices may be exchanged or guidance will be given how to correctly use the technology.
c. Final satisfaction surveys on the participant's experience about collection of digital biomarker data will be completed by participants and by support persons on the tablet computers used for the electronic clinical outcome (eCOA) assessments.
d. Completion of in-clinic assessments can be done either at baseline or on Day 1.
e. At-home active tests will be done once a week.

Table 4 Schedule of Use of Technology for Digital Biomarkers

Activity type	Activity description	Duration	Frequency
Smartphone data collected through user interaction (Active Tasks)[a]	*EQ-5D-5L*	*2 minutes*	*Monthly*
	Three tasks that capture data relevant to core and associated symptoms of ASD	5 minutes	*Weekly*
	Recording of a conversation between the support person and study participant	5 minutes	Weekly
Data collected without user interaction (Passive Monitoring)	Body movement, location, sleep and physiological recording	Continuous	Daily

a *Three* Active Tasks should be completed each *week* by the study participant. In addition, the support person should record a conversation with the study participant at least once per week and complete a numerical response scale to evaluate conversation quality. Active Tasks can be performed at days and times which the study participant and/or support person deem convenient. Study participants are strongly encouraged to *choose a regular day each week to complete all tasks*, adhere to this schedule and collect as much data as they are able to. If participants find the schedule too burdensome, they may choose to reduce the assessment frequency without violating the protocol.

2. INTRODUCTION

2.1 STUDY RATIONALE

The objectives of this Phase 2 proof-of-concept study (BP41316) are to investigate the efficacy, safety, and tolerability of RO7017773 in adolescents and adults (15 to 45 years of age) with autism spectrum disorder (ASD), with a target on the core symptoms of ASD of social communication deficits, and restricted and repetitive behaviors (RRBs) and interests. In addition, a set of biomarkers linked to the mechanism of action of the study drug or to ASD-related alterations will be investigated in a representative patient population to pilot the idenfitication of responder subgroups (see Section 8.7.1.3 and Section 8.7.1.4). To date, very few studies have investigated the effect of pharmacological treatments on the core symptoms of ASD and no pharmacological agents are approved.

A key challenge in the development of new therapies to treat the core social symptoms in ASD is the change of symptoms across different stages of development in longitudinal studies (Sarrett and Rommelfanger 2015) in both social deficits as well as in RRB. The presentation of RRB is known to be associated with age and level of intellectual functioning (Lam and Aman 2007, Esbensen et al 2009, Richler et al 2010, Kim and Lord 2010). Thus, interventional treatment may have different effects, depending on age and intelligence quotient (IQ), in individuals with ASD. Hence, treatment effects in older adolescents and adults may not be extrapolated to effects in the pediatric population, given the potential difference in manifestations of both social skills and RRB with age.

Adolescents and adults aged 15 to 45 years with ASD will be enrolled in this study to allow for the generation of data on the safety and tolerability and the potential efficacy in these age groups.

The rationale for the study design is provided in Section 4.2.

2.2 BACKGROUND

2.2.1 Background on Disease

Autism spectrum disorder (ASD) is a group of heterogeneous neurodevelopmental disorders (NDDs) characterized by two core domains: impairments in social interaction and communication as well as presence of restrictive and repetitive behaviors, interests, or activities (American Psychiatric Association, 2013). Recently the prevalence of diagnosis of ASD in the U.S. has been reported to be 1.68% (1 in 59) in children of 8 years of age (Baio et al 2018) or 2.79% in children from 3 to 7 years of age (Xu et al 2019). In Europe, the prevalence of ASD is within the same range with 1 in 100 people (Elsabbagh et al 2012).

Core symptoms of ASD affecting domains of socialization, communication, and repetitive behavior are usually observed by 3 years of age, although typical language development might delay identification of symptoms. Deficits in socialization manifest themselves as

impaired use of non-verbal communication, delayed and reduced interactions with peers, absent sharing of enjoyable experiences and interest with peers, and lack of social judgment. Abnormalities in communication include a delay in verbal language development, impaired expressive language, deficient language pragmatics, as well as stereotyped, repetitive, or idiosyncratic use of language.

Restricted and repetitive behaviors (RRB) include a broad category of behaviors ranging from stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases); insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day); and highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests) (Levy et al 2009, American Psychiatric Association 2013). RRBs have been conceptually and empirically grouped into at least two subtypes: 'lower order' and 'higher order' behaviors (Szatmari et al 2006, Bishop et al 2006, Turner 1999, Cuccaro et al 2003, Richler et al 2007, Richler et al 2010). Lower order behaviors are motor actions (i.e., stereotyped movements, repetitive manipulation of objects, and repetitive forms of self-injurious behaviors) that are characterized by repetition of movement. Higher order behaviors consist of more complex or 'higher order' cognitive behaviors (i.e., compulsions, rituals and routines, insistence on sameness, and circumscribed interests) that are characterized by a rigid adherence to some rule or mental set (e.g., needing to have things "just so"). Some studies have found more than two subtypes (Lam et al 2008), highlighting the heterogeneity of the presentation of RRBs.

Existing research suggests that level of functioning and age are associated with variations in the manifestation of RRBs in individuals with ASD: Certain domains of RRB, e.g., motor stereotypies, are associated with the presence of intellectual disability (ID), while other domains, e.g., repetitive speech, are associated with higher levels of cognitive functioning (Bishop et al 2006, Militerni et al 2002). Other forms of RRB (such as insistence on sameness or the need for routines) have not been shown to be related to level of intellectual functioning (Militerni et al 2002). Regarding age, RRB symptoms were found to be less severe among older than younger individuals with ASD (Seltzer et al 2003, Shattuck et al 2007). Data also suggest different age-related patterns for the various types of RRBs (Lam and Aman 2007). For example, stereotyped movements and restricted interests appear to be less frequent among older individuals, self-injurious behaviors and compulsive behaviors appear comparable across age groups and ritualistic/sameness appears to be more frequent among older individuals. In a comparison of younger and older children with ASD, younger children were more likely to exhibit motor and sensory repetitive behaviors, and older children were more likely to exhibit more complex repetitive behaviors (Militerni et al 2002). In addition, in ASD

without a comorbid diagnosis of ID, adolescents exhibit fewer stereotyped movements than children and a comparable level of stereotyped movements as adults (Esbensen et al 2009). This pattern is similar to what is observed in comparisons of toddlers and older children (Bishop et al 2006).

RRBs are often the first observable manifestation of ASD during early development and there is evidence that the presence of RRB can negatively impact the learning (Koegel and Convert 1972, Varni et al 1979, Pierce and Courchesne 2001) and socialization (Loftin et al 2008, Nadig et al 2010) of individuals with ASD. Furthermore, research provides evidence that these behaviors also affect family functioning and well-being, often leading to increased stress levels in the family (Gabriels et al 2005, Bishop et al 2007, Lounds et al 2007, Shattuck et al 2007), with parents commonly reporting that RRB symptoms are among the most difficult aspects of ASD they have to tackle on a daily basis, and this in turn engenders more negative parenting styles (South et al 2005).

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

At present, no pharmacological treatment exists for the core deficits of ASD, and currently available treatments address only associated symptoms and comorbidities. (Wink et al 2010). Non-pharmacological treatments have been developed to address the core symptoms; however, efficacy has not been proven in large clinical studies.

Several clinical studies are ongoing for the investigation of agents such as vasopressin agonist and antagonist or bumetanide to address the core symptom of social communication in ASD. However, efficacy in confirmatory Phase 3 clinical studies remains to be established. Furthermore, currently there are no ongoing clinical studies investigating RRBs.

Accordingly, there is a large unmet medical need for pharmacological treatments of these key deficits associated with ASD.

2.2.2 The Role of the GABAergic System in Autism Spectrum Disorder

There is growing evidence that the GABAergic system, the main inhibitory neurotransmitter system in the brain, plays a key role in the pathophysiology of ASD and NDDs by causing an imbalance between excitatory and inhibitory neurotransmission (Braat and Kooy 2015, Ali Rodriguez et al 2018). Gamma-aminobutyric acid type A ($GABA_A$) receptors are ligand-gated chloride channels, with 19 genes encoding for $GABA_A$ receptor subunits that assemble as pentamers with the most common stoichiometry of two α, two β and one γ subunit. $GABA_A$ subunit combinations give rise to functional, circuit, and behavioral specificity (Sieghart 2006, Vithlani et al 2011).

$GABA_A$ receptors that contain the α5 subunit ($GABA_A$ α5) are of particular interest because of their restricted pattern of expression and unique physiological and pharmacological properties (Möhler 2011, Sur et al 1999). The $GABA_A$ α5 subunit-containing receptors are preferentially localized in the hippocampus, prefrontal cortex, nucleus accumbens, insula cortex and amygdala, key regions believed to be involved in the neuropathology and pathophysiology of ASD and other NDD and psychiatric disorders (Mendez et al 2013, Myers et al 2017), thus optimally positioned to dampen cortical outflow and normalize behavioral phenotypes.

Maturation of the GABAergic system includes changes in the expression of GABA receptors, GABA synthesizing enzymes and GABA reuptake transporters as well as chloride transporters such as Na-K-Cl cotransporter 1 and K-Cl cotransporter 2 that control intracellular chloride levels in GABAergic neurons (Kilb 2012, Ben-Ari et al 2012), high intracellular levels of chloride are linked to depolarization of the cell membrane and excitation, and lower intra-cellular chloride levels are linked to hyperpolarization and inhibition. The transition of GABAergic neurons from excitatory to inhibitory begins shortly after birth and is thought to be complete by age 2 years (Ben-Ari et al 2012, Le Magueresse and Monyer 2013). $GABA_A$ α5 subunit expression is high at birth and decreases during first months of life while the appearance in the expression of the $GABA_A$ α1 subunits increases in parallel. Both in rodent and human the relatively high expression of GABAA α5 sustains primarily in the limbic system including the hippocampal region (Laurie et al 1992, Liu et al 1998, Yu et al 2006). In human higher expression is also observed in amygdala and nucleus accumbens as mentioned earlier (Myers et al 2017).

2.2.3 Background on RO7017773

RO7017773 is a small molecule, selective $GABA_A$ α5 subunit-containing receptor positive allosteric modulator (PAM) with the potential to normalize GABAergic signaling in key brain regions implicated in ASD without the side effects of non-selective GABA modulators (e.g., benzodiazepines). RO7017773 is being developed to target the core social, communication, and repetitive behavior impairments of ASD. For details see RO7017773 Investigator's Brochure.

2.2.4 Results from Previous Nonclinical Studies

[redacted]

[redacted]. These results, with recent published data showing that $GABA_A$ $\alpha 5$ receptor deficiency causes autism-like behaviors in mice, including reduced social contacts (Zurek et al 2016), support the use of RO7017773 for the treatment of core symptoms in ASD.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.2.5 Results from Previous and Ongoing Clinical Studies

To date, experience with RO7017773 is limited to 5 completed Phase I clinical studies, all in healthy participants: an entry into human (EIH) single-ascending/multiple-ascending dose (SAD/MAD) study (BP40091), a PET study (BP40257) to assess RO7017773 of brain α5-containing GABAA receptors, a DDI study (BP40822) to investigate the effect of CYP3A inhibitors on the pharmacokinetics of RO7017773, a relative bioavailability (BA) study (BP40950) to compare the Phase II tablet formulation to the Phase I capsule formulation, and a DDI study (BP41921) to investigate the effect of CYP3A induction or CYP2C8 inhibition on the PK of RO7017773.

[redacted]

[redacted]

[redacted]

2.2.5.1 Safety and Tolerability in Healthy Participants

2.2.5.1.1 Summary

To date, a total of 159 healthy participants had received single and multiple oral doses of RO7017773 in the completed Phase I Studies (BP40091, BP40257, BP40822, BP40950, and BP41921; see Table 5). [redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

2.2.5.1.2 Review of Adverse Events of Somnolence and Sudden Onset of Sleep

[redacted]

[redacted]

2.2.5.1.3 Gastrointestinal Adverse Events

[redacted]

[redacted]

2.3 BENEFIT/RISK ASSESSMENT

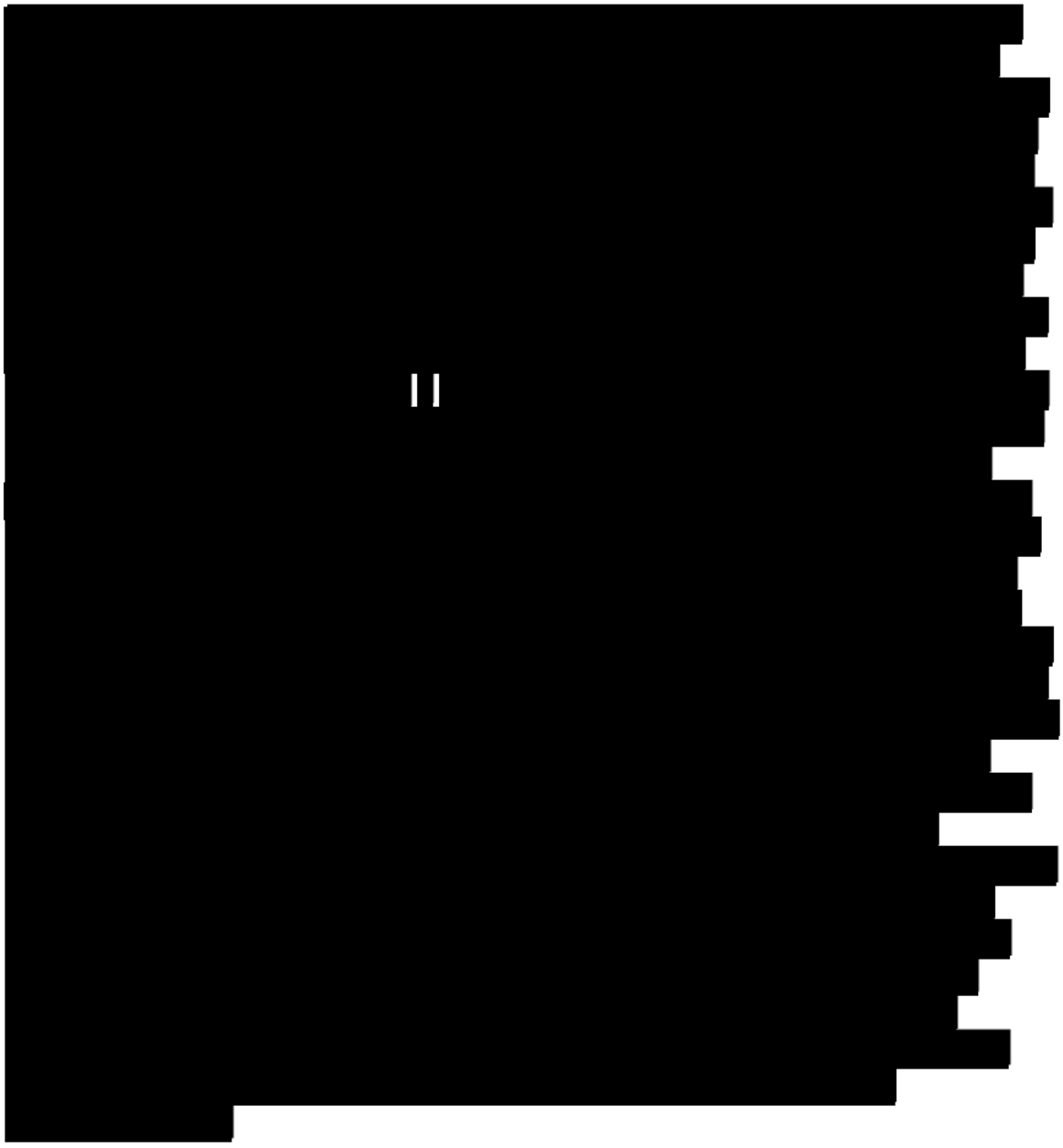
There is a high unmet medical need for effective pharmacotherapies in the treatment of core symptoms of ASD. Current primary treatment emphasizes forms of behavioral interventions (e.g., applied behavior analysis) to advance development and adaptive and social skills, but also various pharmacological treatments to target maladaptive co-occurring conditions (psychostimulants, alpha agonists, antidepressants, and antipsychotics) (Zwaigenbaum et al 2015). To date, no efficacious pharmacotherapy for the core symptoms of ASD exists (Ji and Findling 2015).

The GABAergic system, the main inhibitory neurotransmitter system in the brain, has been hypothesized to play a key role in the pathophysiology of ASD and other NDD and psychiatric disorders and to constitute a promising target of pharmacological treatment (Mendez et al 2013). However, non-selective $GABA_A$ modulators (e.g., benzodiazepines), have a safety profile that does not provide a positive risk-benefit ratio for long-term treatment of ASD symptoms and other NDDs (O'Brien 2005). $GABA_A$ α5 subunit-containing receptors, which constitute about 5% of all $GABA_A$ receptors, are preferentially localized in key regions believed to be involved in the neuropathology and pathophysiology of ASD and may be optimally positioned to dampen cortical outflow and normalize behavioral phenotypes (Cheng et al 2018). As such, RO7017773 as a $GABA_A$ α5 PAM, has the potential to normalize GABAergic signaling without the side effects of non-specific $GABA_A$ modulators with a prospect of benefit for ASD.

All data available for RO7017773 are summarized in the current Investigator's Brochure. Guidance to the Investigator, Section 6 of the Investigator's Brochure summarizes the potential risks to participants following treatment with RO7017773 and the specific tests, observations and precautions that are required for clinical studies.

[redacted]

[redacted]



Considering nonclinical findings and existing clinical results with RO7017773 (see Section 2.2.4 and Section 2.2.5), the key elements of risk management in the proposed study are summarized below:

- Informed selection of 2 doses levels with favorable safety and tolerability (AEs of mild severity and no clinically significant changes in QTc)
- Communication of potential risks and precautions in the study protocol and participant Informed Consent Form (ICF)
- Appropriate inclusion/exclusion criteria in the study protocol
- Stepwise approach to enroll participants (high-functioning adults [IQ ≥70] first, then low-functioning adults and high- and low-functioning adolescents [IQ ≥ 50 to 69]) (see Section 4.1)
- Restrictions on concomitant medications (e.g., medications of strong CYP3A4 inhibitors and inducers will be prohibited co-medication in order to control for major PK variations) (see Section 6.5).
- Implementation of dosing stopping rules (see Section 4.1.2)
- Involvement of an Internal Monitoring Committee (IMC) and a Scientific Oversight Committee (SOC) for periodic review of the study data (see Section 4.1.3)
- Safety monitoring and a phone call on Day 7 to assess for any clinically significant symptoms and/or new medication (see Section 1.3)
- Sleep monitoring, daytime sedation, increased incidence of somnolence and sudden onset of sleep will be monitored through non-serious adverse event of special interest (NSAESI) reports, attention/sleepiness and sleep questionnaires, neurocognitive tests of attention and digital biomarker assessment. Flexibility in dosing such as switching dosing from morning to evening intake during the periods between site visits could be allowed in case of frequent incidence of sedation after discussion with the Sponsor's Medical Monitor (see Section 8.3.6)
- Monitoring of gastrointestinal related events through NSAESI reports (see Section 8.3.6)
- Assessment of cognitive functions to characterize effects of chronic dosing (see Section 8.1.5.10).
- Safety follow-up visits to evaluate the tolerability to the withdrawal of RO7017773 at the timepoints specified in the SoA (Section 1.3).

In addition, the protocol includes a stopping rule for dosing when QTcF measurement exceeds a limit of 480 ms confirmed in repeat measurement within 30 minutes (see Section 4.1.2). This criterion has been set to a more conservative value than typically used in clinical trials (i.e., 500 ms) as per ICH Topic E14 (Section 2.1.2. Safety Monitoring, and Discontinuation Criteria). The rationale for this lower threshold for discontinuation is based on the assessment of risk-tolerance level in this trial: although the potential for RO7017773 to increase QTc is not expected at the doses used in BP41316, participants with ASD are likely to use concomitant medications such as antipsychotics with a potential effect of QTc prolongation. With a stopping rule fixed at 480 ms, the Sponsor has fixed the QTc inclusion criterion to a maximum of 450 ms irrespective of sex in order to have a margin between the inclusion threshold and the stopping criterion.

In summary, RO7017773 has the potential of improving social communication and repetitive and restricted behaviors in individuals with ASD. Safety and tolerability in healthy volunteers did not reveal a drug-associated safety pattern considered prohibitive for Study BP41316. Safety monitoring will focus on AE reporting, cardiovascular and laboratory parameters. Also included are assessments of somnolence, sleep propensity, cognition, anxiety, and suicidality. Safety monitoring will be supplemented by stopping rules for individual participants (see Section 4.1.2) and assessed on predefined timepoints or on an ad hoc basis by an IMC and SOC (see Section 4.1.3). Upon review of data by the IMC and SOC and if no safety signal is observed in the initial high-functioning adult participants, the enrollment of the (high- and low-functioning) adolescents and low-functioning adults will start. On the basis of the neurodevelopmental nature of the disorder, the mechanism of action, the observed clinical safety and tolerability, and the potential of RO7017773 to address a large unmet need in individuals with ASD, the risk-benefit ratio is deemed acceptable for the clinical development of RO7017773, also taking into account that the study will include participants with intellectual disabilities and participants younger than 18 years of age.

An assessment was conducted to determine whether there is any impact of the COVID-19 pandemic on the benefit/risk assessment of this study protocol including but not limited to the patient population under study and study treatment being evaluated. On the basis of that assessment, no impact is anticipated and the existing safety monitoring and management guidelines, and risk mitigation measures provided in the study protocol are considered adequate.

On the basis of mode of action of RO7017773, together with clinical experience to date, there is no evidence to suggest that administration of RO7017773 would affect the efficacy of SARS-CoV-2 vaccinations or worsen the AEs experienced in response to the vaccinations. Additionally, there is no expected interaction between RO7017773 and SARS-CoV-2 vaccines. Therefore, the currently effective protocol-mandated safety monitoring and risk mitigation measures are considered satisfactory in the context of conducting the study with the concomitant use of SARS-CoV-2 vaccines in participants.

As with any other medications, SARS-CoV-2 vaccines should be reported as concomitant therapy by using the standard fields in the clinical database (see Section 6.5). Any AE due to the vaccination and any symptomatic treatment (e.g., with analgesic and/or antipyretic medicinal products) should be adequately reported as AEs.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RO7017773 is provided in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 6.

Table 6 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 12-week treatment with RO7017773 compared with placebo in treating social communication deficits in participants with Autism Spectrum Disorder (ASD)	• Change from baseline to Week 12 in the Adaptive Behavior Composite score of the Vineland™ Adaptive Behavior Scales, Third Edition (Vineland™-3)
Secondary	
• To evaluate the safety and tolerability of a 12-week treatment with RO7017773 in 15- to 45-year-old participants with ASD.	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs). • Incidence of treatment discontinuations due to AEs • Change from baseline over time and incidence of clinically relevant abnormalities in vital signs including orthostatic changes, ECG parameters and safety laboratory values including the incidence of marked laboratory abnormalities • Change from baseline over time in suicide risk (using the Columbia-Suicide-Severity Rating Scale [C-SSRS]) • Incidence of daytime sleepiness assessed with the Karolinska Sleepiness Scale (KSS), the Epworth Sleepiness Scale (ESS) or the ESS for children and adolescents (ESS-CHAD), and the Sudden Onset of Sleep Questionnaire
• To evaluate the efficacy of a 12-week treatment with RO7017773 compared with placebo on restricted and repetitive behaviors (RRBs)	• Change from baseline to Week 12 in behavior/symptoms as measured by all domains of the Repetitive Behavior Scale-Revised (RBS-R) scale
• To evaluate the efficacy of a 12-week treatment with RO7017773 compared with placebo on social behaviors	• Change from baseline to Week 12 on the Vineland-3 Socialization domain
• To evaluate the efficacy of a 12-week treatment with RO7017773 compared with placebo on communication skills	• Change from baseline to Week 12 on the Vineland-3 Communication domains

Table 6 Objectives and Endpoints (cont.)

Objectives	Endpoints
Exploratory	
• To investigate the pharmacokinetics (PK) in 15- to 45-year-old participants with ASD and exposure-response relationships of RO7017773	• Plasma concentration per timepoints specified in the SoA (Section 1.3) • Other PK parameters as appropriate
• To evaluate the efficacy of a 12-week treatment with RO7017773 compared with placebo on RRBs	• Change from baseline to Week 12 on the Caregiver-Reported Routines Inventory (CRRI) scale
• To explore the effects of a 12-week treatment with RO7017773 compared with placebo on global clinical severity and symptoms of ASD	• Change from baseline to Week 12 o on the Clinical Global Impression Scale – Improvement (CGI-I) and Clinical Global Impression Scale – Severity (CGI-S) o on the Beck Anxiety Inventory (BAI) o on the Parent Rated Anxiety Scale-ASD (PRAS-ASD) o on the Adolescent/Adult Sensory Profile™ questionnaire o on the Short Sensory Profile (SSP-2) – (mandatory for adolescents and optional for low-functioning adults) o on the Patient-Reported Outcomes Measurements Information System (PROMIS) Sleep Disturbance short form 8 items o on the PROMIS Sleep-Related Impairment short form 8 items
• To explore the acute (Day 1), subchronic (2-week) and chronic (12-week) effects of RO7017773 compared with placebo on PD biomarkers	• Change from baseline to Weeks 2 and 12 and change on Day 1 from pre- to post-dosing in resting state EEG power in the beta band (12-30 Hz), and *change from baseline to Weeks 2 and change on Day 1 from pre- to post-dosing in* saccadic peak velocity (SPV).
• To explore the effects of a 12-week treatment with RO7017773 compared with placebo on neuronal responses to *face viewing*	• Change from baseline to Week 12 in EEG response to *faces* (including the N170 of the Event Related Potential to faces)

Table 6 Objectives and Endpoints (cont.)

Objectives	Endpoints
Exploratory (cont.)	
• To explore the effects of a 12-week treatment with RO7017773 compared with placebo on eye-tracking biomarkers related to ASD	• Change from baseline to Week 12 in Gaze pattern related to social preference in visual scenes
• To explore the effects of a 12-week treatment with RO7017773 compared with placebo on metabolic and molecular dynamics	• Change from baseline to Week 12 in the hair exposome
• To explore the overall genetic risk for ASD and treatment response with RO7017773	• ASD polygenic risk score and genetic $GABA_A$ score derived from genetic sample to predict treatment response
• To assess health-related quality of life in individuals with ASD as reported by parent/support person over a 12-week treatment period	• Change from baseline to Week 12 in PedsQL™ Quality of Live Inventory *Generic Core Scale*
• To assess effects on cognition over a 12-week treatment period	• Change from baseline to Week 12 in Cogstate neurocognitive battery with a focus on attention/reaction time, verbal learning and working memory) • Change from baseline to Week 12 in PedsQL™ Cognitive Functioning Scale
• To explore the effects of a 12-week treatment with RO7017773 compared with placebo in core and associated symptoms of ASD as measured by digital biomarkers and to evaluate the feasibility of implementation of digital biomarkers in a clinical study setting	• Change from baseline to Week 12 in core and associated symptoms of ASD (including sociability, communication deficits, restricted and repetitive behaviors, spatial working memory, anxiety and sleep) as measured remotely with digital health technology • Adherence to the digital biomarker schedule of assessments between baseline and Week 12

Feedback from support persons or parents will be collected with entry and exit questions at baseline and at the end of the study, respectively.

4. STUDY DESIGN

4.1 OVERALL DESIGN

An overview of the study design is provided in Figure 1.

Study BP41316 is a multicenter, randomized, double-blind, parallel-group, 3-arm, placebo-controlled, 12-week treatment Phase II study to investigate the efficacy, safety and tolerability, and pharmacokinetics of RO7017773 in participants aged 15 to 45 years with a diagnosis of ASD and a Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) score of ≥ 50.

Approximately 105 participants with ASD (in order to have at least 84 evaluable participants at study end) aged 15 to 45 years will be enrolled into the study. Participants will be randomized [redacted] in a 1:1:1 ratio (35 participants randomized to each treatment arm).

After approximately 18 high-functioning (WASI-II ≥70) adults (aged 18 to 45 years) have completed 6 weeks of treatment [redacted] the IMC, together with the SOC will conduct a PK, safety, and tolerability review. Once adequate PK, safety, and tolerability in high-functioning adults have been established and PK-model predictions from healthy adult volunteers are confirmed to be comparable with the PK results in high-functioning adults, then low-functioning adults ([LFAs]; WASI-II ≥ 50 to 69) and adolescents aged 15 to 17 years (both high- and low-functioning) will be included in the study.

A second IMC + SOC review will be performed to evaluate PK, safety, and tolerability data from all available participants once at least 12 adolescents have completed 2 weeks of treatment. Details are provided in Section 4.1.3 and Section 6.3.1.

Randomization will take place on Day 1 after a screening period of at least 2 to up to 4 weeks, and after a pre-baseline and a baseline visit as indicated in the SoA. Randomization to the different treatment arms will be stratified by age and IQ.

Each participant will be evaluated using several scales and tests at each visit at the clinic. A total of 9 clinic visits (screening period included) and 1 phone contact, to assess for any clinically significant symptoms and/or new medication, are planned (see Section 1.3). In addition, digital biomarker data will be collected from all participants.

Each participant will need a reliable caregiver, parent, or support person who will oversee the participant's adherence with protocol-specified procedures and provide feedback on all informant- based assessments throughout the study. The same support person must attend all on-site visits. *For support persons of high-functioning adult participants, no on-site visits are necessary after the screening visit if the support persons opt to complete all electronic clinical outcome assessments (eCOA), interview, and forms remotely (see Appendix 1 Section 2.1.2.2).*

Interim analyses will be performed as outlined in Section 9.5.

4.1.1 Length of the Study

The total duration of the study for each participant will be up to 24 weeks (approximately 5.6 months), divided as follows:

- Screening period of at least 2 weeks and up to 4 weeks
- Study pre-baseline and baseline period (2 weeks)
- Study treatment period with fixed dose (12 weeks)
- Safety and efficacy follow-up period (6 weeks).

4.1.2 Individual Stopping Criteria

Dosing will be stopped at any time during the study in a given individual participant if one of the following circumstances occurs, unless it is determined by the Investigator that the occurrence is not related to the administration of the study drug:

- **QTc:** A confirmed QTcF (average of triplicate values) above 480 ms or a change from baseline by more than 60 ms (when confirmed in repeat measurement within 30 minutes), will result in drug interruption. For the assessment of the QTcF stopping rule, central ECG readings should be used to determine whether the criteria have been met. An expedited review by the central vendor should be requested by the Investigator to ensure that the results are available before the next administration of the study drug. If the central readings are not available at the time of next dosing, this stopping criterion will apply. Study drug may be resumed with the joint agreement of the Investigator and the Sponsor's Medical Monitor when follow-up test results show that the participant no longer meets the dose interruption criteria.
- **Liver safety:** Any participant with the occurrence of either of the following liver values will be discontinued:
  - ALT or AST >3 x ULN and bilirubin >2 x ULN
  - ALT or AST >3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
- **Other** findings which, at the joint discretion of the Sponsor's Medical Monitor, the Sponsor Safety Science Leader and the Investigator, indicate that dosing in this individual should be stopped (e.g., severe sedation/somnolence, cognitive impairment) (see also Table 10).

Ultimately and in case of disagreement, the Investigator remains responsible for the decision to stop dosing.

4.1.3 Administrative Structure

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

An IMC consisting of a selected subset of Roche representative(s) as identified in the "IMC Agreement" will be responsible to perform interim analyses of accumulated safety, tolerability, PK, and efficacy (as required) data. The IMC members, the clinical

pharmacologist, and the pharmacometrician will be unblinded to individual study treatment allocation (see Section 6.3 for treatment allocation and blinding of data).

An SOC consisting of at least one external expert will support the IMC in making their recommendations. These SOC members will likewise be unblinded to individual study treatment allocation.

Access to treatment assignment information will follow the Sponsor's standard procedures (see Section 6.3).

On the basis of accumulated study data available at their review, the IMC and SOC may recommend adjustment(s) of the dose levels, dosing regimen, or the timing of dosing (see Section 6.6).

Further details can be found in the "IMC Agreement" and in Section 9.5 (Interim Analyses).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

4.2.1 Rationale for Study Population

The population selected for this study consists of male and female participants aged 15 to 45 years with ASD according to Diagnostic and Statistical Manual of Mental Disorders, Edition 5 (DSM-5) criteria and confirmed by Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) and with an IQ score of ≥50.

Individuals meeting ASD social communication thresholds on the Autism diagnostic observational scale (ADOS), with an SRS ≥ 66 and the presence of RRBs will be recruited to allow the monitoring of these behaviors during the study. To this aim, only participants with a Children's Yale-Brown Obsessive Compulsive Scale modified for Autism Spectrum Disorder (CY-BOCS-ASD) total score of at least *8* at screening will be enrolled.

The upper age limit has been incorporated on the basis of the need for input from informants, such as parents, who have knowledge of the development history of the study participants for the diagnostic assessment for ASD.

The adolescent group has been selected for this study because of the fact that the presentation of RRBs in this age group may be more similar to those of adults than of younger children. Furthermore, because ASD is an NDD, it is conceivable that early treatment intervention may not only help to reverse deficits, but may also prevent further insult caused by the abnormal brain development (Krueger and Bear 2011) and maturation.

A comorbid diagnosis of ID (IQ <70) is frequently related to greater severity of autism symptoms, poorer overall developmental outcome, and a decreased likelihood of improvement in cognitive and language skills with behavioral interventions than for a diagnosis of ASD without ID (Lord and Bailey 2002, McGovern and Sigman 2005, Nordin and Gillberg 1998, Seltzer et al 2004, Shea and Mesibov 2005). Low-functioning participants (defined per protocol as IQ ≥ 50 to 69 at screening; also referred to as LFs) who meet the inclusion/exclusion criteria could also benefit from the treatment with RO7017773. Thus, it is desirable to study the treatment effects on both high-functioning and low-functioning participants. Participants with an IQ < 50 will be excluded, because of the higher prevalence of significant comorbidities in this population and because they are expected to have difficulties with understanding the study (in order to provide assent for participation) and completing the participant-reported study assessments.

Individuals with confirmed or suspected chromosome 15q11.2-q13.1 duplication syndrome (Dup15q syndrome) are excluded because of their chromosomal alterations that may lead to elevated expression of $GABA_A$ α5 subunit-containing receptors and therefore potentially increased effects of the study drug (see Section 5.2).

Randomization will be staggered to ensure safety, tolerability, and PK data in high-functioning adult participants before the enrollment of adolescent participants and low-functioning adult participants.

Participants will be randomized [redacted] at a ratio of 1:1:1.

Recruitment of the following subpopulations will be limited across treatment arms:

- Adults (aged 18 – 45 years) will be limited to a maximum of 75% of the total sample size to ensure at least 25% adolescents (aged 15 – 17 years) will be recruited.
- Female participants up to a maximum of 25% of the sample size, because of the increased prevalence of ASD in male participants compared with female participants (4:1; CDC 2018); thus mirroring the presentation of ASD.
- Low-functioning participants with an IQ ≥ 50 to 69 will be limited to a maximum of 25% of the total sample size to allow for a focused analysis to high-functioning participants.

4.2.2 Rationale for Control Group

In addition to the two active study groups receiving either [redacted] of RO7017773, a placebo group will be used as a control. The rationale for using a placebo as control group is the lack of approved medications for treating the core symptoms of ASD.

4.2.3 Rationale for Biomarker Assessments

4.2.3.1 Rationale for Pharmacodynamic Biomarkers

PD biomarkers measure a neurophysiological effect of the drug. They are used to quantify the strength of the drug effect (acute and chronic) in a given participant and have applications in demonstrating modulation of brain activity, translation between different species, clinical populations, or demographic groups and stratification. This study includes two PD biomarkers for which a PD response to RO7017773 has been demonstrated in BP40091 after 1, 7 or 13 days of dosing: (1) resting state EEG (EEG beta power), and (2) electrooculogram ([EOG]) for SPV.

4.2.3.2 Rationale for Response Biomarkers

Response Biomarkers measure aspects of behavior or brain function that are related to the symptoms that are intended to be improved with treatment. This study will perform task-based EEG and eye tracking to evaluate the impact of RO7017773 on activity in brain networks that support functions and viewing behavior related to ASD symptoms targeted by the treatment (social *and* restricted interests).

4.2.3.3 Rationale for Hair Biomarkers

The chemical analysis of hair samples, including simultaneous assessment of multiple biochemical pathways, provides a longitudinal trace of chemicals and metabolites over time. These data may allow stratification of the heterogeneous participant population and will be used to identify potential responder subgroups with similar metabolic or biochemical profiles. In addition, the temporal dynamics of drug uptake and metabolism may be assessed by monitoring the plasma concentrations of RO7017773 and its metabolites in hair samples. Optional hair samples will also be collected from support persons who provide consent on the applicable ICF. These optional hair samples will serve as a control to assess the potential contribution of shared environmental factors in the exposome analysis.

4.3 JUSTIFICATION FOR DOSAGE SELECTION AND TREATMENT DURATION

The trajectory of a potential pharmacological treatment-induced improvement of social communication deficits and/or RRB in ASD is unknown. One multicenter study has been published so far, showing significant pharmacological effects on communication and social behaviors in ASD as measured by the Vineland™ Adaptive Behavior Scales, Second Edition (Vineland™-II) after 12 weeks of treatment (Bolognani et al 2019). In addition, a post-hoc analysis from a Phase II study has suggested a benefit of arbaclofen on socialization assessed by the Vineland™ -II socialization domain in a subgroup of individuals with ASD after a 12-week treatment period (Veenstra-VanderWeele et al 2016). Behavioral interventions have also shown benefits. For example, Virues-Ortega reported a systematic review and meta-analysis of the effect of the TEACCH program (Virues-Ortega et al 2013). Some of the studies included in this review used the Vineland™-II scale. The duration of those studies ranged from 10 to 36 weeks, suggesting that the minimum length of a study that aims to detect gains in adaptive behaviors in ASD participants as measured by the Vineland™-II should be within this range. The recently developed Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) assesses the same adaptive behavior domains and contains a number of additional items, especially for easier/easier skills (Farmer et al 2020). Very similar adaptive behaviors are measured; therefore, the minimal study length to detect changes is expected to be comparable. Because clinically meaningful effects may take some time to emerge, a 12-week treatment period for RO7017773 has been chosen to permit observation of potential behavioral changes in social communication, RRBs, and functional outcomes, as well as to characterize the safety and tolerability profile of RO7017773. A 12-week treatment duration is also supported by the 13-week repeat dose toxicity studies that have been conducted as part of the nonclinical safety program (see Section 2.2.4).

For dose modifications see Section 6.6.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study will be considered to be the date of the last visit (including the last follow-up visit) of the last participant in the study (last participant last visit [LPLV]).

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

Male and female participants aged 15 to 45 years with ASD according to DSM-5 who fulfill all the inclusion criteria listed in Section 5.1 and for whom none of the exclusion criteria listed in Section 5.2 apply will be included in the study.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

The final decision on whether a participant will enter the randomized, double-blind treatment period will be made by the Principal Investigator in accordance with the protocol. An Eligibility Assessment Form (EAF, see Section 8.11.1) will be completed as part of the screening process and forwarded to an external vendor and Medical Monitor in order to help ensure all relevant information has been taken into account.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Study participants or legal representatives should be able and willing to provide written informed consent or assent, as applicable and as per local requirements according to International Council for Harmonisation (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the participant according to ICH and local regulations and assent must be given whenever possible. The ability to provide informed consent for each participant will be based on the Principal investigator's clinical judgment.

2. Availability of a parent or other reliable support person who is fluent in local language and has frequent and sufficient contact with the participant. The same person must agree to accompany the participant to all clinic visits and provide information about the participant's behavior and symptoms and must agree to oversee the participant's adherence with protocol-specified procedures and study medication dosing.

- *For support persons of high-functioning adult participants, no on-site visits are necessary after the screening visit if all eCOA assessments, interview, and forms are performed remotely (see Section 4.1 and Appendix 1 Section 2.1.2.2).*

Age

3. Age 15 to 45 years, at the time of signing the informed consent or assent form.

Type of Participants and Disease Characteristics

4. Males and female participants with Autism Spectrum Disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

    - For transgender participants, the Investigator should consult with the Medical Monitor or delegate to assess potential safety concerns or interference with safety and efficacy testing. Transgender participants will be enrolled by their biological sex.

    Note: It is important that a high-confidence autism diagnosis has been established by an autism expert prior to screening and is supported by medical records.

5. Social Responsiveness Scale, Second Edition (SRS-2) (T-score)≥66.

6. Wechsler Abbreviated Scale of Intelligence (WASI-II) or equivalent assessment ≥50 at screening or within the last 12 months prior to screening *(for adults within the last 5 years prior to screening if the assessment was done at age 18 or older)*. The proportion of low-functioning participants (IQ ≥ 50 to 69) will be limited to 25% overall.

    - If a previous assessment is used, the Investigator should assess whether it has been performed by an appropriately qualified rater.

7. ASD or Autism diagnosis confirmed by Autism Diagnostic Observation Schedule (ADOS-2), done by a certified rater at screening, or within the last 6 months prior to screening.

8. Presence of at least moderate to severe repetitive behaviors as per Children's Yale-Brown Obsessive Compulsive Scale modified for ASD (CY-BOCS-ASD) total score of at least *8* at screening.

Weight

9. Body mass index (BMI) within the range of 18.5 to 40 kg/m^2 (inclusive).

Sex

10. Male and female participants with contraception requirements.

The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

a) Female Participants

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Women of non-childbearing potential (WONCBP), as defined in Appendix 5.
- Women of childbearing potential (WOCBP), who:
  - Agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods (hormonal or non-hormonal) that result in a failure rate of <1% per year during the treatment period and for at least 28 days after the last dose of study drug. Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices (see Appendix 5).

    Hormonal contraceptive methods must be supplemented by a barrier method (as defined in Appendix 5; preferably condom with a spermicide) if participants are receiving any drug known to reduce the effect of hormonal contraception (including anti-epileptic drugs inducing drug metabolism). In such a situation, the risk assessment should be discussed with the Medical Monitor.

    Note: Females who reach menarche after enrollment in the study must agree from this time forward to regular blood or urine pregnancy testing as defined in the SoA and must agree to either remain completely sexually abstinent or comply with the same contraceptive requirements as outlined above for WOCBP from first menses until 28 days after the last dose of study treatment (see Appendix 5).

b) Male Participants

Male contraception is not required in this study because of the minimal seminal dose transmitted through sexual intercourse (Banholzer et al 2016, Appendix 5).

Additional Inclusion Criteria:

11. Language, hearing, and vision compatible with the study measurements as judged by the Investigator. Non-verbal individuals will be excluded from study participation.

12. Allowed existing treatment regimens should be stable for 8 weeks prior to screening except:

    - 6 weeks for non-pharmacological interventions
    - 12 weeks in the case of antipsychotic therapies
    - 6 months for antiepileptic treatments

    Investigator expects stability of these treatments and behavioral interventions for the duration of the study.

13. In the Investigator's opinion, able to participate and deemed appropriate for participation in the study, capable of following the study SoA and able to comply with the study restrictions

14. In the Investigator's opinion, participation in the study or discontinuation of prohibited medication will not pose undue risks.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

Neurologic/psychiatric conditions

1. Presence of chromosome 15q11.2 q13.1 duplication syndrome (Dup15q syndrome), known "syndromic" forms of ASD *(confirmed per genetic results available at screening):* fragile X syndrome, Prader Willi syndrome, Rett's syndrome, tuberous sclerosis, *and Angelman syndrome, as well as genetic alterations strongly associated with ASD per genetic results available at screening affecting the following genes: CHD8, ANDP, SHANK3.*

    - Clinical suspicion of the presence of Dup15q syndrome should lead to study exclusion. Please contact the Medical Monitor for any questions related to a clinical suspicion of Dup15q syndrome.
    - *Other genetic information available at screening should be taken into consideration for assessment of participant eligibility. The Principal Investigators are encouraged to consult with the Sponsor (Medical Monitor or designee) for advice.*

2. Medical history of alcohol and/or substance abuse/dependence in the last 12 months or positive test for drugs of abuse at screening (unless the finding is related to the intake of concomitant medications allowed by the protocol).
3. Initiation of a major change in psychosocial intervention (including investigational) within 6 weeks prior to screening. Minor changes in ongoing treatment (e.g., missed therapy sessions due to holiday/vacation; planned break in therapy due to holidays; changes in college/university programs) are not considered major changes.
4. Clinically significant psychiatric and/or neurological disorder that may interfere with the safety or efficacy endpoints.
    - Participants with a psychiatric diagnosis other than ASD, including but not limited to, bipolar disorder, psychosis, schizophrenia, post-traumatic stress disorder or major depressive disorder will be excluded if the psychiatric comorbidity has the potential to confound results or impact safety.
    - Participants with non-suicidal self-injurious behaviors (e.g., cutting, head banging) that interferes with safety and efficacy testing will be excluded.
5. Risk of suicidal behavior in the opinion of a certified clinician or as evidenced by a "yes" to questions 4 and/or 5 of Columbia-Suicide-Severity Rating Scale (C-SSRS) taken at screening and baseline with respect to the last 12 months or period since the screening visit, respectively, or any suicide attempt in the past 5 years.
6. Unstable epilepsy/seizure disorder within the past 6 months.

<u>Cardiovascular conditions</u>

7. Concurrent cardiovascular disease considered not well controlled by drug treatment, including participants with clinically significant bradycardia and arrhythmias, myocardial infarction within 12 months of screening or uncompensated heart failure.
8. Confirmed clinically significant abnormality on 12-lead electrocardiogram (ECG), including a QTcF of ≥450 ms (based on the average of 3 consecutive measurements). Central ECG readings should be used to determine if this criterion is met.
9. Congenital heart diseases not treated and congenital QTc prolongation or family history of Long QT Syndrome.

<u>Other conditions</u>

10. Medical history of malignancy if not considered cured or if occurred within the last 3 years with the exception of fully excised non-melanoma skin cancers or in-situ carcinoma of the cervix that has been successfully treated.
11. Concomitant disease, condition or treatment which would either interfere with the conduct of the study or pose an unacceptable risk to the participant in the opinion of the Investigator

12. Known active or uncontrolled bacterial, viral, or other infection (excluding fungal infections of nail beds) or any major episode of infection or hospitalization (relating to the completion of the course of antibiotics) within 6 weeks prior to the start of drug administration.

Prior/Concomitant Therapy

13. Use of prohibited medications or herbal remedies (with the exception of herbal remedies approved by the Medical Monitor or designee) within 6 weeks or 5 half-lives ($t_{1/2}$) prior to randomization (whichever is longer).

Prior/Concurrent Clinical Study Experience

14. Donation or loss of blood over 500 mL in adults and 250 mL in adolescents within 3 months prior to randomization.
15. Participation in an investigational drug study within 1 month or 5 times the $t_{1/2}$ of the investigational molecule (whichever is longer) prior to randomization or participation in a study testing an investigational medical device within 1 month prior to randomization or if the device is still active.
16. Sensitivity to any of the study treatments or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study.

Diagnostic Assessments

17. Confirmed clinically significant abnormality in hematological, chemistry or coagulation laboratory parameters.
18. Positive test result at screening for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV, untreated), or human immunodeficiency virus (HIV)-1/2. HCV participants who have been successfully treated and who test negative for HCV RNA, may be considered eligible for entry into the study.

Other Exclusions

19. Uncorrected hypokalemia or hypomagnesaemia.

5.3 LIFESTYLE CONSIDERATIONS

[redacted]

Participants above the legal age for alcohol consumption who drink alcohol should agree to avoid consuming alcohol as much as possible and in any case not exceeding 1 drink per week (see Appendix 7) during the study. Because of the agonistic effect of alcohol on the $GABA_A$ receptor, alcohol consumption should be avoided during the week preceding any clinical assessments (i.e., for one week).

If participants feel that they are not sufficiently well, especially during the first week of taking the study drug, they should not engage in hazardous activities requiring complete mental alertness such as operating machinery, driving a car or riding a bicycle until it is known how RO7017773 affects them. This applies also if they feel unwell later during the study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but fail to be randomized to study treatment within 8 weeks. Screen failures may be tracked separately.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Screen-failed participants can be re-screened after discussion with the Sponsor (Medical Monitor or designee) if there is a substantial change in the participant's general condition (e.g., a new medication will be stable from now on for at least 8 weeks at re-screening or an active infection has resolved) and if recruitment for the study is still ongoing. Re-screening will not be allowed if the participant failed earlier to meet the disease-specific inclusion criteria (e.g., CY-BOCS-ASD, ADOS-2, SRS-2, or WASI-II; see Section 5.1) *except for participants who did not meet the CY-BOCS-ASD (or CGI) inclusion threshold under a previous version of the protocol with a score that now would meet the revised inclusion threshold.*

Re-screening is allowed for participants who were screened in the study and met study inclusion/exclusion criteria (exception: exclusion criterion #12 for active infections) but failed to be randomized within the maximal 8-week screening and pretreatment window because of a study halt, or logistical, personal, or technical reasons. In these cases, an abbreviated re-screening consisting of written informed consent, medical history, physical examination, substance use, alcohol test, laboratory safety, coagulation, serology, urinalysis, and inclusion/exclusion criteria will need to be performed. Abbreviated re-screening will be permitted only in cases where this poses no safety risk to the participant. At no time should the duration between the original screening visit and the abbreviated re-screening visit exceed 3 months.

6. TREATMENTS

Study intervention is defined as any investigational product (including placebo) or marketed product intended to be administered to a study participant according to the study protocol.

All investigational medicinal products (IMPs) required for completion of this study (RO7017773 and placebo identical in appearance to RO7017773) will be provided by

the Sponsor. First administration of study drug will be at the study center under supervision of site staff.

Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated AEs, should be reported as described in Appendix 2, Section 5.2.

6.1 TREATMENTS ADMINISTERED

Table 7 summarizes the treatments administered. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively. Please see RO7017773 Investigator's Brochure for more details.

Table 7 Summary of Treatments Administered

Study Treatment Name:	RO7017773	Matching placebo to RO7017773
IMP and NIMP	IMP	IMP
Dose Formulation:	[redacted] tablets	[redacted] tablets
Unit Dose Strength(s)/Dosage Level(s):	20 mg	NA
Dose:	[redacted]	
Route of Administration:	Oral	Oral
Dosing instructions:	[redacted]	
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling:	[redacted]	

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the Roche clinical study supplies department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study medication will be in accordance with the Sponsor's standard and local regulations.

The study site should follow all instructions included with each shipment of IMP. The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

The study site (i.e., Investigator or other authorized personnel [e.g., pharmacist or nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Study Monitor upon discovery.

The qualified individual responsible for dispensing the study treatment will dispense the pack(s) according to the numbers issued by the interactive (voice/web) response system (IxRS).

The Investigator or delegate must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form. Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual (if appropriate) and/or the RO7017773 Investigator's Brochure for information on IMP formulation, IMP handling, including preparation and storage, and accountability.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

Randomization will take place on Day 1. To ensure balanced enrollment to respective cohorts, randomization to the different treatment arms (placebo, [redacted] RO7017773 or [redacted] RO7017773 [redacted] with a ratio of 1:1:1) will be stratified by age and IQ, and capping rules will be applied as follows:

Table 8 Capping Rules

Clinical Factor	Capping Rule
• Age 15 to 17 years vs 18 to 45 years	• The proportion of adults (18 to 45 years) will be limited to 75% overall.
• IQ (as assessed by WASI-II) ≥50 to 69 vs ≥ 70	• The proportion of low-functioning participants (IQ≥50 to 69) will be limited to 25% overall.
• Sex female vs male	• The proportion of female participants will be limited to a maximum of 25%.

In addition, randomization will be staggered with the enrollment of high-functioning adults (IQ ≥ 70) first, followed by adolescents and low-functioning adults (IQ <70). After approximately 18 high-functioning adults have completed 6 weeks of treatment [redacted] the IMC + SOC will conduct a PK, safety and tolerability review.

All participants will be centrally assigned to randomized study treatment using an IxRS. Before the study is initiated, the telephone number and call-in directions for the IxRS and/or the log in information and directions for the IxRS will be provided to each site.

Study treatment will be dispensed at the study visits summarized in SoA.

Returned study treatment should not be re-dispensed to the participants.

The randomization list will be computer generated centrally by a third party and made available only to those individuals responsible for PK sample bioanalysis and to statisticians or programmers at the Sponsor directly involved in the production of outputs to support IMC and SOC meetings. The data will be analyzed in a secure area which is not accessible to any blinded personnel.

6.3.2 Blinding

The IxRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the Investigator, it is in the participant's best interest to know the study treatment assignment. The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (e.g., antidote available). In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and Clinical Study Report (CSR), as applicable.

Unblinding should not result in the withdrawal of the participants from the study. Every effort should be made to retain unblinded participants.

If unblinding is necessary for participant management (in the case of an SAE), the Investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the study treatment for any other reason, he/she should contact the Medical Monitor directly. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to an SAE).

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected SAEs (see Section 8.3.4) that are considered by the Investigator to be related to study treatment.

Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the study medication according to the randomization schedule. This individual will write the date, number of bottles dispensed and participant number on the study treatment bottle, label and Drug Accountability Record. This individual will also record the number of tablets received by each participant during the study.

Compliance regarding administration of study medication at home will be monitored by the completion of a medication diary by the participants (or the support persons as applicable).

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including approved over-the-counter [OTC] or prescription medicines, as well as approved dietary, herbal, and nutritional supplements) used by a participant from 12 weeks prior to screening until the follow-up visit must be recorded on the Concomitant Medications electronic Case Report Form (eCRF) along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency).

Any non-pharmacological interventions (as defined in Section 6.5.2) must be recorded on the appropriate eCRF.

All medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Therapy

Participants must be on a stable prescribed medication regimen for 8 weeks before screening, with the exception of antipsychotic therapies and antiepileptic treatments (where participants need to be on a stable regimen for at least 12 weeks and 6 months before screening, respectively; see inclusion criterion *12* in Section 5.1). Any stable prescribed medication at screening should remain stable throughout the study. All changes in prescribed medication need to be discussed with the Sponsor (Medical Monitor or designee).

Examples of Allowed Medications:

- Selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI) antidepressants including fluoxetine (see also inclusion criterion in Section 5.1)
- Melatonin
- Trazodone (at low doses) for insomnia
- Aripiprazole
- Risperidone
- Psychostimulants (e.g., methylphenidate)
- Clonidine
- Occasional use of paracetamol/acetaminophen
- Antiepileptic medication (except carbamazepine and phenytoin, which are prohibited because of CYP3A induction) must be stable for 6 months (see also inclusion criterion *12* in Section 5.1)

- Benzodiazepines with a short $t_{1/2}$ (e.g., lorazepam, alprazolam, or oxazepam) are allowed if
  - taken only on an as needed (PRN) basis,
  - limited to 3 times per week,
  - prescribed for short-term or intermittent medical conditions and,
  - not taken immediately before the assessments visits (i.e., not within 2 days or within 5 times the elimination $t_{1/2}$, whichever is longer before a scheduled visit).

  Note: for benzodiazepines with a long $t_{1/2}$ (except for benzodiazepines to treat emerging symptoms of rebound and/or withdrawal effects) see Section 6.5.3.

- Drugs known to prolong QTc interval will be allowed if stable at screening provided the screening QTc does not meets exclusion QTc criterion (see list of drugs known to prolong QTc in Appendix 8).
- Any medication for medical illnesses other than ASD not listed under prohibited medications
- Vaccines, including those against COVID-19

Any other medications require the approval from the Investigator and the Sponsor's Medical Monitor (or designee).

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

6.5.2 Non-Pharmacological Interventions

Non-pharmacological interventions (e.g., participant psychotherapy, cognitive behavioral therapy, applied behavioral analysis, speech therapy, occupational therapy, rehabilitative therapy, and social skills training) must be stable for 6 weeks prior to screening and must remain stable throughout the ongoing study in terms of type of intervention and intensity. Minor changes in ongoing treatment (e.g., missed therapy sessions due to holiday/vacation; planned break in therapy due to school holidays; changes in college/school programs) are not considered significant and need not to be discussed with the Sponsor (Medical Monitor or designee).

A complete history of non-pharmacological interventions for the treatment of ASD including all previously completed therapies will be reported on eCRF and will include start and end date, name of therapy and number of hours per week.

6.5.3 Prohibited Therapy

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, oral contraceptives, hormone-replacement therapy, or other maintenance therapy (as listed in Section 6.5.1) unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Use of the therapies listed below (e.g., prescription drugs, OTC drugs, herbal remedies, nutritional supplements) is prohibited during the study and for at least 6 weeks prior to randomization (or within 5 times the elimination $t_{1/2}$, whichever is longer) to ensure washout of medication and until follow-up, unless otherwise specified below.

Examples of prohibited medications (see also Appendix 6):

- Strong inhibitors of CYP3A4/5 (e.g., ketoconazole, clarithromycin, grapefruit juice)
- Strong inducers of CYP3A4 (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's Wort)
- Under no circumstances should a strong CYP3A4 inhibitor be given in combination because of the potential increase in exposure. If the use of a strong inhibitor is indicated, the Investigator should contact the Sponsor to discuss alternative options (e.g., replacement of clarithromycin by azithromycin, which is not a CYP3A4 inhibitor). For certain cases, the Sponsor may advise pausing the treatment with RO7017773 and restarting when the CYP3A4 inhibitor has been discontinued and 5 times the elimination $t_{1/2}$ of the CYP3A4 inhibitor have elapsed.
- Chronic adrenocorticoid or glucocorticoid use (use of inhaled and topical formulations are allowed)
- *Regarding the use of* anxiolytics, sedatives, and hypnotics: benzodiazepines with a long $t_{1/2}$ or benzodiazepine-like drugs pharmacologically similar to benzodiazepine (e.g., zolpidem, zopiclone, eszopiclone, and zaleplon) will not be allowed during screening and treatment periods (for benzodiazepines with a short $t_{1/2}$ that are allowed see Section 6.5.1.

  In case of emerging symptoms of rebound and/or withdrawal effects of the study drug during the follow-up period after end of treatment at Week 12, treatment with benzodiazepines is allowed (see Section 8.3.7) and must be reported on the appropriate section of the eCRF.

- Barbiturates and opioids
- Alcohol consumption – more than 1 drink per week (see Section 5.3)
- Other GABA agonists (direct/indirect): tiagabine, vigabatrin, baclofen, phenelzine, *topiramate, felbamate, zonisamide, pregabalin*
- Valproic acid and its salts
- Oxytocin
- Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP])
- All other psychotropic medications or medications used for a psychotropic effect (unless allowed by the Medical Monitor or designee)
- Tetrahydrocannabinol due to its psychoactive effects (e.g., marijuana)
- Herbal and dietary supplements including cannabidiol (unless allowed by the Medical Monitor or designee)

- Non-pharmacological interventions cannot be initiated after randomization (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy).

The above list of medications is not exhaustive. The Investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with the study drug. In addition, the Investigator should contact the Medical Monitor or designee if questions arise regarding medications not listed above.

[redacted]

6.6 DOSE MODIFICATION

Participants will be randomized to receive either [redacted]

Dependent on the safety observations, the timing of dosing or the dose level may be adjusted during the treatment period (see Section 4.1.3 and Section 8.3.7.2). In addition, a different dosing regimen may be explored if warranted on the basis of the safety profile of RO7017773 (e.g., exploration of dose titration or tapering). This would be done on the basis of IMC and SOC recommendation and after discussion with the Sponsor's Medical Monitor.

6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor does not intend to provide RO7017773 or other study interventions to participants after conclusion of the study or any earlier participant withdrawal.

7. DISCONTINUATION OF STUDY, STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to

motivate participants to comply with all the study-specific procedures as outlined in this protocol.

Details on study and site closures are provided in Appendix 1 Study Governance Considerations Study.

7.1 DISCONTINUATION OF STUDY TREATMENT

For data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed, see the SoA (Section 1.3).

Reasons for discontinuation of study treatment (or withdrawal from the study) may include but are not limited to the following:

- Participant unable to continue to comply with the study treatment and study requirements
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Any event that meets the stopping criteria defined in Section 4.1.2
- Specific adverse events if discontinuation of treatment is required to manage the event

Every effort should be made to obtain information on participants who withdraw from the study treatment but have not withdrawn consent. Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit and may undergo follow-up assessments (see Section 8.11.3), unless the participant withdrew consent. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

7.1.1 Temporary Interruption

If study treatment administration is delayed by more than 3 days relative to the scheduled administration date, this will be considered a treatment interruption. Administration may resume at the next planned dosing date. A missed dose of study treatment will not be made up.

Before permanently discontinuing study treatment (regardless of whether initiated by the participant, the Investigator or Sponsor), an interruption should be considered.

Temporary study drug interruption is an acceptable method to manage AEs related to any of the study treatments. Participants who have temporarily interrupted study treatment

should be considered for restarting as soon as medically justified in the opinion of the Investigator.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of samples donated to the Research Biosample Repository (RBR).

Participants who withdraw from the study will not be replaced.

For data to be collected at the time of study discontinuation and at safety and follow-up visits and for any further evaluations that need to be completed, see SoA (Section 1.3).

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timepoints are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study treatment.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time-frame defined in the SoA.

8.1 EFFICACY ASSESSMENTS

The primary objective of this study is to evaluate the efficacy of a 12-week treatment with RO7017773 compared with that of placebo in socialization and communication in adults aged 18 to 45 years and adolescents aged 15 to 17 years with ASD, as measured by the change from baseline on the composite of the Vineland™-3.

Secondary efficacy objectives are the evaluation of a 12-week treatment with RO7017773 compared with placebo on restricted and repetitive behaviors, social behaviors, and communication skills.

All assessments (see Table 9) will take place at the timepoints specified in Section 1.3.

Table 9 Overview Clinical Scales/Clinical Outcome Assessments

Scale group	Specific scale	High-functioning		Low-functioning		Administration	Respondent	Time [min]
		Adolescents	Adults	Adolescents	Adults			
Assessments During Screening (Section 8.1.4)								
WASI-II		Mandatory	Mandatory	Mandatory	Mandatory	Clinician	Participant	~ 30
ADOS-2		Mandatory	Mandatory	Mandatory	Mandatory	Clinician	Participant	~ 35 – 40
SRS-2		Mandatory	Mandatory	Mandatory	Mandatory	eCOA	Support person	~ 15 – 20
CY-BOCS-ASD		Mandatory	Mandatory	Mandatory	Mandatory	Central rater	Support person and participant	~ 20
Clinical Outcome Assessments (Section 8.1.5)								
Vineland-3		Mandatory	Mandatory	Mandatory	Mandatory	Central rater	Support person	45 – *80*
Repetitive Behavior	RBS-R	Mandatory	Mandatory	Mandatory	Mandatory	eCOA	Support person	~ 15
	CRRI	Mandatory	Mandatory	Mandatory	Mandatory	eCOA	Support person	~ 17
CGI-S interview		*Mandatory*	*Mandatory*	*Mandatory*	*Mandatory*	*Clinician*	*Support person and participant*	*~ 30*
CGI-S / CGI-I (after initial *pre-baseline* interview)		Mandatory	Mandatory	Mandatory	Mandatory	Clinician	Support person and participant	~ 15 (combined)
Anxiety	BAI	Mandatory	Mandatory	NA	NA	eCOA	Participant [1]	~ 5
	PRAS-ASD	Mandatory	NA	Mandatory	Mandatory	eCOA	Support person	~ 10
Sensory Sensitivities	AASP	Mandatory	Mandatory	NA	NA	eCOA	Participant [1]	10 – 15
	SSP-2	Mandatory	NA	Mandatory	Mandatory	eCOA	Support person	~ 7
PedsQL	Generic Core and Cognitive Functioning Scales	Mandatory	Mandatory	Mandatory	Mandatory	eCOA	Participant for HF adults and HF adolescents Support person for all LF.	~ 10

Table 9 Overview Clinical Scales/Clinical Outcome Assessments (cont.)

Scale group	Specific scale	High-functioning		Low-functioning		Administration	Respondent	Time [min]
		Adolescents	Adults	Adolescents	Adults			
Neurocognitive Battery	DET	Mandatory	Mandatory	Mandatory[3]	Mandatory[3]	Clinician	Participant	~ 3
	IDN	Mandatory	Mandatory	Mandatory[3]	Mandatory[3]	Clinician	Participant	~ 3
	OCL	Mandatory	Mandatory	Mandatory	Mandatory	Clinician	Participant	~ 6
	ONB	Mandatory	Mandatory	Mandatory[3]	Mandatory[3]	Clinician	Participant	~ 4
	TWOB	Mandatory	Mandatory	Mandatory	Mandatory	Clinician	Participant	~ 4
	ISL	Mandatory	Mandatory	Mandatory	Mandatory	Clinician	Participant	~ 15 (total for 3 parts)
	CPAL	Mandatory	Mandatory	Mandatory	Mandatory	Clinician	Participant	~ 7
	GMLT	Mandatory	Mandatory	Mandatory	Mandatory	Clinician	Participant	~ 7
Somnolence and Sudden Onset of Sleep	KSS	Mandatory	Mandatory	Mandatory	Mandatory	eCOA	Participant for HF adults Support person for all others [2]	~ 5
	ESS	NA	Mandatory	NA	NA	eCOA	Participant	~ 5
	ESS-CHAD	Mandatory	NA	Mandatory	Mandatory	eCOA	Support person	~ 5
	Sudden Onset of Sleep Questionnaire	Mandatory	Mandatory	Mandatory	Mandatory	Clinician	Participant for HF adults Support person for all others [2]	~ 5

Table 9 Overview Clinical Scales/Clinical Outcome Assessments (cont.)

Scale group	Specific scale	High-functioning		Low-functioning		Administration	Respondent	Time [min]
		Adolescents	Adults	Adolescents	Adults			
Sleep	PROMIS Sleep Disturbance	Mandatory	Mandatory	Mandatory	Mandatory	eCOA	Participant for HF adults and HF adolescents [1] Support person for all adolescents and all LF	~ 5
	PROMIS Sleep-Related Impairment	Mandatory	Mandatory	Mandatory	Mandatory	eCOA	Participant for HF adults and HF adolescents [1] Support person for all adolescents and all LF	~ 5
Entry and Exit Questions		NA	NA	NA	NA	eCOA	Support person	~ 5

AASP = Adolescent/Adult Sensory Profile; ADOS-2 = Autism Diagnostic Observation Schedule, Second Edition; BAI = Beck Anxiety Inventory; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; CPAL = Continuous Paired Associate Learning Test; CRRI = Caregiver-Reported Routines Inventory; CY-BOCS-ASD = Children's Yale-Brown Obsessive Compulsive Scale Modified for ASD; DET = Detection Test; eCOA = electronic clinical outcome assessment; ESS = Epworth Sleepiness Scale; ESS- CHAD = Epworth Sleepiness Scale for Children and Adolescents; GMLT = Groton Maze Learning Test; HF = high-functioning participant; IDN = Identification Test; ISL = International Shopping List Test; KSS = Karolinska Sleepiness Scale; LF = low-functioning participant; NA = not applicable; OCL = One Card Learning Test; ONB = One Back Test; PedsQL = Pediatric Quality of Live Inventory; PRAS-ASD = Parent-rated Anxiety Scale for ASD; PROMIS = Patient-Reported Outcomes Measurements Information System; RBS-R = Repetitive Behavior Scale-Revised; SRS-2 = Social Responsiveness Scale, Second Edition; SSP-2 = Short Sensory Profile 2; TWOB = Two Back Test; Vineland-3 = Vineland Adaptive Behavior Scales, Third Edition; WASI-II = Wechsler Abbreviated Scale of Intelligence, Second Edition.

1 If the participant is not able to complete the self-reported scale, the support person-reported form/scale will be used, i.e., PRAS-ASD instead of BAI; SSP-2 instead of AASP; PROMIS proxy-forms instead of PROMIS self-reported forms.

2 If the KSS or Sudden Onset of Sleep Questionnaire is reported by the support person this has to be done together with the study participant. Sudden Onset of Sleep Questionnaire is administered as an interview.

3 For LF participants, the selection of attention tasks (detection, identification, and one back tests) should be prioritized and performed first. All effort should be made to also collect the remainder of the tasks if the study participant is able to comply.

An external company(ies) and external consultants will provide training to all raters on the various scales and will provide all sites with the relevant record forms, instruction manuals, and kits as appropriate. Training and requirements on rater qualifications are described separately in the external company(ies)' documentation.

For some electronic clinical outcome assessments (eCOAs) audio recordings may be captured. These audio recordings will be reviewed by central raters to verify whether these scales were administered according to the rating standards. If necessary, raters will be contacted for remediation and additional training.

Remote centralized ratings for the Vineland™-3 scale (see Section 8.1.5.1) and the CY-BOCS-ASD (see Section 8.1.4.4) will be carried out via live secure videoconference. The interview for the Vineland-3 scale will be audio-recorded for quality purposes.

The centralized rater may be observed by another clinician for quality control purposes. If a remote administration session cannot occur for an unforeseen reason, it will be rescheduled.

It is not planned to extract any information about the participant and support person from these video or audio recordings.

8.1.1 Requirements for Support Persons

Each participant will need a reliable caregiver, parent, or support person (moving forward they will be deemed the "support person"). The same support person will provide feedback on all informant- based assessments throughout the study and the same person must attend all on-site visits. If a support person visit cannot be completed as arranged (e.g., the support person is delayed in transit) visits should be rescheduled as soon as possible after the original appointment within the specified time window, *or incomplete or missing eCOA assessment may be completed remotely (see Appendix 1, Section 2.1.2.2). For support persons of high-functioning adult participants, no on-site visits are necessary after the screening visit if all eCOA assessments, interview, and forms are performed remotely (see Appendix 1, Section 2.1.2.2).*

In the Investigator's opinion, the support person should be deemed appropriate to participate in the study and able of following the applicable study procedures, including participation in video calls with the central rater for the Vineland-3 and CY-BOCS-ASD assessments.

The support person must live with the participant or have substantial and sufficient periods of contact with the participant (see below) and is willing and able to attend the on-site visits when required. The support person must oversee the participant's

adherence with protocol-specified procedures, and report on the participant's status via completion of study assessments.

If the support person does not live with the participant, the Investigator has to be satisfied that the participant can contact the support person readily during the times when the support person is not with the participant. If in doubt about whether a participant's care arrangements are suitable for inclusion, the Investigator should discuss this with Sponsor (Medical Monitor or designee). A non-cohabitating support person must spend sufficient time with the participant so that, in the opinion of the Investigator, the support person can reliably assess the participant's mental status, activities and behavior, and report on the participant's adherence and health. This would normally be possible when the support person spends a few hours with the participant every day.

The support person arrangements for participants living in a residential home need to be assessed carefully on a case by case basis:

- A staff member of the residential home can be the support person if this person spends sufficient time with the participant. In the opinion of the Investigator, the support person must be able to reliably assess the participant's mental status, activities, and behavior, and report on the participant's adherence and health. This would normally be possible when the support person spends a few hours with the participant every day.
- A family member living at the participant's home can be the support person if the participant returns home every night. When the participant only returns home over the weekend, a family member can be the support person only if they have intensive interaction with the participant during the week e.g., via phone calls, calls via Skype, SMS messages, etc. The quality of these interactions between support person and participant needs to be assessed for each participant to determine whether the level of interaction is sufficient.
- A family member cannot be the support person when the participant lives full time in the residential home, unless the family member spends a few hours in the residential home with the participant every day.

If in doubt about whether a participant's care arrangements are suitable for inclusion, the Investigator should discuss this with the Sponsor (Medical Monitor or designee).

8.1.2 Instructions for Support Person

Because of the important role of the support persons as the respondents in several key assessments, they will be provided with instructions on their role in the study as well as background information on ASD symptoms and behaviors at screening (see SoA in Section 1.3) by the Investigator. This aims to help them report accurately on the

participant's health and behaviors and mitigate the risk of overt placebo response. Instructions will also be provided at the baseline and Week 12 visits prior to the administration of clinical scales.

The instructions will take approximately 5 to 10 minutes.

8.1.3 Administration of Participant-Reported Scales to Illiterate Participants

For participants who are illiterate or have reading deficits the following procedure for the mandatory participant-reported scales should be used:

- The scale administrator will read out the questions and answers and show the answers on the Rater station.
- The participant will choose one of the possible answers on the Rater station.

If the participant is still unable to complete the scale even with the described assistance, the scale will be skipped.

8.1.4 Screening Assessments

The following assessments will be performed at screening to check the participant's eligibility for this study.

8.1.4.1 Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II)

The WASI-II is a tool used to evaluate an individual's cognitive functioning and generate IQ scores (Wechsler 1999, Wechsler 2011) and will be administered by a qualified rater at screening. If the WASI-II or an equivalent assessment (e.g., the Wechsler Adult Intelligence Scale [WAIS]) has been performed by an appropriately qualified rater and documented within 12 months of the screening visit *(within 5 years prior to screening for adults if the assessment was done at the age of 18 years or older)*, there will be no requirement to repeat it.

The assessment will take approximately 30 minutes to complete.

8.1.4.2 Autism Diagnostic Observation Schedule, Second Edition (ADOS-2)

The ADOS-2 is a diagnostic tool used to document the presence of ASD (Gotham et al 2007, Lord et al 2000). 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. Only qualified ADOS-2 raters are allowed to perform the ADOS-2 to confirm eligibility of participants.

The ADOS-2 includes four modules for use with different age groups and language levels; modules 2, 3, and 4 will be used in this study. The appropriate module of the ADOS-2 will be administered by a certified rater at screening.

The assessment will take approximately 35 to 40 minutes to complete.

8.1.4.3 Social Responsiveness Scale, Second Edition (SRS-2)

The SRS-2 is a 65-item informant-based rating scale designed specifically for use in ASD to quantitatively measure an individual's ability to engage in emotionally appropriate reciprocal social behavior in a naturalistic social setting (Constantino 2005). Each item on the scale enquires about an observed aspect of reciprocal social behavior that is rated on a scale from 1 (not true) to 4 (almost always true). Social skill levels are assessed over five domains: Social Awareness, Social Cognition, Social Communication, Social Motivation, and Autistic Mannerisms. The total score generated serves as an index of severity of social deficits in the autism spectrum. The SRS-2 total score is expressed in raw and T-scores. Raw scores are converted to T-scores for gender and respondent. T-scores of 66 through 75 are interpreted as indicating moderate deficiencies in reciprocal social behavior that are clinically significant and lead to substantial interference in everyday social interactions. A total T-score of 76 or higher is considered to indicate severe deficiencies and strongly associated with clinical diagnosis of autistic disorder (Wilkinson 2017).

The support person will complete the rating scale at screening. A clinician will be available to assist the support person during completion of the questionnaire.

This assessment will take approximately 15 to 20 minutes to complete.

8.1.4.4 Children's Yale-Brown Obsessive Compulsive Scale Modified for ASD (CY-BOCS-ASD)

The CY-BOCS-ASD is a modified version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), for children and adolescents with ASD. The interviewer asks the support person about past and present repetitive behaviors, guided by the revised repetitive behavior checklist (Scahill 2014). It contains a list of 25 behaviors, classified into the following categories: hoarding/ritualistic behavior, sensory-motor and arranging, insistence on routines, self-injurious behaviors, stereotypy, and restricted interests. This checklist was expanded from the original version to include repetitive behaviors commonly seen in children with ASD. A target symptom list comprising the four most troublesome behaviors is established by the interviewer. The severity (0 to 4) of each target behavior is rated for the following five items: time spent, interference, distress, resistance, and degree of control to generate a total score (0-20). Two additional items

(repetitive behavior-free interval and peculiarity) are also rated but are not included in the total score.

The ratings evaluate the symptom severity over the past week and are based on the information collected from the participant and support person during the interview. The final rating is based on the clinical judgment of the central rater.

The interview should take approximately 20 minutes to complete.

8.1.5 Clinical Outcome Assessments

All assessments will take place at the timepoints specified in the SoA in Section 1.3.

Support persons, clinicians and participants will use an electronic device to capture clinical outcome assessments (COAs) specified in the sections below (see also Appendix 1, Section 2.1.2.1). The specific sequence of assessments will be predefined on the electronic device for each participant and should be followed throughout the study.

Any entries on COA should be reviewed for completeness by site staff during the visit and support person and participants should be requested to complete any blank items. If a scale cannot be completed during the visit or for a scale, the total score (e.g., the composite scores for Vineland™-3) cannot be calculated with the available data, it should be attempted to repeat the scale during an unscheduled visit as soon as possible (within the next 7 days).

8.1.5.1 Vineland Adaptive Behavior Scale, Third Edition (Vineland™-3)

The Vineland™ is an instrument that measures communication, daily living skills, socialization, motor skills (only used in children up to 9 years of age) and maladaptive (not assessed in this study) behaviors of individuals with developmental disabilities (Sparrow et al 2005). The Comprehensive Interview will be administered to a participant's support person in this study, during which the rater or clinician will ask to the support person open-ended questions relating to the participant's activities and behavior. Domain scores will be obtained for the individual domains of Socialization, Communication, and Daily Living Skills and used to calculate the Vineland™ Adaptive Behavior Composite score. Standardized scores on the Adaptive Behavior Composite score range from 20 to 160, with higher scores indicating better adaptive functioning.

Vineland™-3 will be administered at different visits (see SoA in Section 1.3) by central raters via live, secure telemedicine platform. For any individual participant, the same rater should administer the Vineland™.

This interview will take approximately 45 to 60 minutes. The rater will interview the support person to complete the Vineland™.

8.1.5.2 Repetitive Behavior Scale-Revised (RBS-R)

The RBS-R is a 43-item informant-based questionnaire, assessing the variety of restricted and repetitive behaviors observed in individuals with ASD (Bodfish et al 2000). The scale is grouped into six subscales: Stereotyped, Self-Injurious, Compulsive, Ritualistic, Sameness, and Restricted Behaviors. Each item utilizes a 4-point response scale assessing the presence and severity of a restricted or repetitive behavior. Response options range from "Behavior does not occur" (0) to "Behavior occurs and is a severe problem" (3). On the last question, participants are asked to “lump together” all of the behaviors described in the questionnaire and provide a rating for how much of a problem these repetitive behaviors are overall, on a scale from 1 to 100: where “1” represents “not a problem at all” and “100” represents “as bad as you can imagine”.

A total score is generated for each subscale and an overall total score encompasses all the subscales. The overall total score ranges from 0 to 129; higher scores are indicative of more severe RRBs.

It will take the support person approximately 15 minutes to complete the RBS-R.

8.1.5.3 Caregiver-Reported Routines Inventory (CRRI)

The CRRI is a caregiver-reported RRB scale for older adolescents and adults based on the Children Routine Inventory-Revised (Evans et al 2017). It has been developed by the author of the Children Routine Inventory-Revised in collaboration with the Sponsor in order to extend the age-range for caregiver-reported Routine Inventory scales to older adults and adolescents. The CRRI questionnaire captures a wide range of RRBs, including stereotypies, tics, compulsions, habits, sensory sensitivities, and focused interests, in the context of typical and atypical development in adults and adolescents (Evans et al 2017). All items will be answered on a five-point Likert scale from “not at all/never,” “a little/rarely,” “somewhat/sometimes,” “quite a lot/often,” and “very much /always.” Forms with appropriate recall periods will be used at the timepoints indicated in the SoA (Section 1.3).

The CRRI scale includes 62 items. It will take the support person approximately 17 minutes to complete the CRRI.

8.1.5.4 Clinical Global Impression-Severity (CGI-S) and Improvement (CGI-I) Scales

The CGI rating scales are tools used to evaluate both the severity of illness and change from Baseline (Guy et al 1976). The CGI-S reflects the rater’s impression of the participant’s current autism severity on a 7-point scale ranging from no symptoms (1) to

very severe symptoms (7). The CGI-I is used to assess the clinical change as compared with symptoms at baseline using a 7-point scale, ranging from very much improved (1) to very much worse (7). For this study, modified versions will be used (Busner and Targum 2007).

For any individual participant, all CGI-S and CGI-I assessments throughout the study should be done by the same clinician.

The first CGI-S assessment at *pre-baseline* requires an extended clinical interview and will take the clinician approximately 30 minutes to complete. At subsequent visits, approximately 15 minutes in total will be needed to complete the CGI-I and the CGI-S.

8.1.5.5 Beck Anxiety Inventory (BAI)

The BAI is a well-validated 21-item participant-administered inventory probing for common symptoms of anxiety (Beck et al 1988). Each item contains four possible responses, which range in severity from 0=not at all (e.g., unable to relax) to 3=severely - it bothered me a lot. Participants are asked to provide answers based on the way they have been feeling over the past month, including the assessment day.

The BAI is a self-administered scale and will take the participant about 5 minutes to complete.

8.1.5.6 Parent-Rated Anxiety Scale-ASD (PRAS-ASD)

The Parent Rated Anxiety Scale for ASD (PRAS-ASD) is a support person-rated scale with 25 items to assess the severity of anxiety symptoms in children and adolescents with ASD. Support persons of adolescent participants will be asked to describe their child's worries and anxiety-related behaviors over the past 2 weeks on a 0- to 3-point scale from "NONE" = "not present", "MILD" = "present sometimes, not a real problem", "MODERATE" = "often present and a problem", and "SEVERE" = "very frequent and a major problem". A publication about the PRAS-ASD is in preparation (as per personal communication, Prof Dr. [redacted]).

The PRAS-ASD will be completed for adolescents. It takes about 10 minutes for a support person to complete.

8.1.5.7 The Adolescent/Adult Sensory Profile

The Adolescent/Adult Sensory Profile (Brown and Dunn 2002) is a judgment-based self-questionnaire consisting of 60 items rated for frequency of the behavior at home or in the community. Items use a 5-point Likert scale and inquire about taste/smell processing, movement processing, visual processing, touch processing, activity level, and auditory processing. Items are factored into four sections: "Low Registration", "Sensation

Seeking", "Sensory Sensitivity", and "Sensation Avoiding". The adolescent/adult form is a unique sensory measure in that it is a self-reported questionnaire.

The questionnaire takes 10 to 15 minutes for the participant to complete.

8.1.5.8 Short Sensory Profile 2 (SSP-2)

The Short Sensory Profile Version 2 (SSP-2; Dunn 2014) is a 34-item parent or support person-reported questionnaire that probes for the effect of sensory processing anomalies on a person's ability to function in daily life. Item responses occur on a five-point Likert-rating scale from 1 (almost never) to 5 (almost always). The SSP-2 was based on the Sensory Processing Framework (Dunn 1999) and provides scores in four quadrants based on the child's neurological threshold to sensory input and their method of self-regulation. The four quadrants are Seeking ("the degree to which a child obtains sensory input"), Avoiding ("the degree to which a child is bothered by sensory input"), Sensitivity ("the degree to which a child detects sensory input."), and Registration ("the degree to which a child misses sensory input.").

The SSP-2 will be performed by support persons of adolescents and low-functioning adults. It will take the support person approximately 7 minutes to complete the SSP-2.

8.1.5.9 Pediatric Quality of Life Inventory™ (PedsQL™) Version 4.0 Generic Core Scale and Cognitive Functioning Scale

The Pediatric Quality of Life Inventory™ (PedsQL™) Version 4.0 Generic Core Scale assessment consists of a 23-item questionnaire encompassing four core scale domains: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items) and School Functioning (5 items). In addition to the four scale scores a Psychosocial Health Summary score, a Physical Health Summary score, and a total score can also be computed by averaging across the relevant domains.

The PedsQL™ Cognitive Functioning Scale, which contains six items, will also be completed. Each item in the PedsQL™ Generic Core and Cognitive Functioning scales utilizes a 5-point response scale ranging from "never (a problem)" (0) to "almost always (a problem)" (4). Items are then reverse-scored and linearly transformed to a 0- to 100-point scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0), i.e., higher scores indicate better quality of life or cognitive function.

The following standard forms with a recall period of one month will be employed in this study (Varni et al 2004): adult self-report (ages 18+, high-functioning), pediatric self-report (adolescents aged 15 to -17 years, high-functioning). In addition, support person-reported forms will be used for all low-functioning participants.

It will take approximately 10 minutes to complete the PedsQL™ Generic Core and Cognitive Functioning scales.

The cognitive tests will be applied as part of the safety assessments (see Section 8.2.7).

8.1.5.10 Neurocognitive Battery

The cognitive tests will be applied as part of the safety assessments (see Section 8.2.7). The total battery takes approximately 45 minutes to perform, the selection of attention tasks (detection, identification, and one back tests) takes approximately 10 minutes to perform.

For low-functioning participants, the selection of attention tasks (detection, identification, and one back tests) should be prioritized and performed first. All effort should be made to also collect the remainder of the tasks if the study participant is able to comply. If not all tasks can be completed, an explanation should be recorded on the "Additional Observations" eCRF.

Two test sessions of shorter duration will be carried out at the pre-baseline visit for habituation to the test environment.

Detection Test (Psychomotor Function)

The Detection Test (DET) is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this test, the playing cards all depict the same joker. The participant is asked to press the "Yes" key as soon as the card in the center of the screen turns face up. The software measures the speed and accuracy of each response.

This assessment takes approximately 3 minutes to perform.

Identification Test (Attention)

The Identification Test (IDN) is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this test, the playing cards are all either red or black jokers. The participant is asked whether the card displayed in the center of the screen is red. The participant responds by pressing the "Yes" key when the joker card is red and No when it is black. The software measures the speed and accuracy of each response.

This assessment takes approximately 3 minutes to perform.

One Card Learning Test (Visual Learning)

The One Card Learning Test (OCL) is a measure of visual learning and uses a well-validated pattern separation paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The participant is asked whether the card displayed in the center of the screen was seen previously in this test. The participant responds by pressing the “Yes” or “No” key. The software measures the speed and accuracy of each response.

This assessment takes approximately 6 minutes to perform.

One Back Test (Working Memory)

The One Back Test (ONB) is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The participant is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The participant responds by pressing the “Yes” or “No” key. Because no card has been presented yet on the first trial, a correct first response is always “No”. The software measures the speed and accuracy of each response.

This assessment takes approximately 4 minutes to perform.

Two Back Test (Working Memory)

The Two Back Test (TWOB) is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The participant is asked whether the card displayed in the center of the screen is the same as the one presented two cards previously. The participant responds by pressing the “Yes” or “No” key. Because no card has been presented two-back on the first and second trials, a correct response on these trials is always “No”. The software measures the speed and accuracy of each response.

This assessment takes approximately 4 minutes to perform.

The International Shopping List Test (Verbal Learning)

The International Shopping Test (ISL) is a measure of verbal learning and uses a well-validated list-learning paradigm. The test is administered using a computer. High frequencies, high imagery, concrete nouns (items from a shopping list) are read to the

participant by the test supervisor at the rate of one word every two seconds. Once all 12 words have been read, the participant is asked to recall as many of the words as he/she can as quickly as possible. The test supervisor uses a mouse or stylus to mark the words recalled by the participant on the computer screen. When the subject can recall no more words, the same list is read a second time. The test supervisor records the words recalled by the participant on this trial. This is then repeated a third time. 30 minutes later: without having the list read again, the participant is asked to recall the words from the list (delayed recall condition). The recall test is followed by a recognition condition test where the test supervisor reads a shopping list item that may or may not have been on the original list and the participant has to respond either affirmatively (if the item was on the original list) or negatively (if it was not). The recall and recognition test is repeated the next day about 24 hours after the list learning. If the clinic visit is split into two days (which is possible for Week 6, Week 12, and 6-week follow-up visits, see SoA in Section 1.3) the repeats are performed at the clinic. If the participant returned home after the first day the repeats are performed over the phone as close in time to the 24h timepoint as possible. In addition, questions about the sleep quantity and quality will be asked. The software registers the number of correct responses as recorded by the test supervisor.

This assessment takes approximately 15 minutes to perform (5 minutes for each of the three parts).

Continuous Paired Associate Learning Test (Paired Associate Learning)

The Continuous Paired Associate Learning Test (CPAL) is a measure of visual associate memory and uses a well-validated paired associate learning paradigm in which the subject must learn the locations of a number of amoeba-like shapes on the computer screen. This test consists of a single amoeboid shape displayed in the center of the screen surrounded by a number of blue- filled circles. Beneath all but two of the blue spheres are amoeboid shapes, one of which matches the central display; the two remaining circles are distractors. In the exposure phase of the test all of the to-be-remembered pattern-location associations are presented on the computer screen simultaneously. After a five second delay, a pattern is shown in the central location and this signals that the subject should touch the location in the periphery that contains the same pattern. This process continues until the participant has acknowledged all of the pattern-location associations. The learning phase begins with the same test display presented during the exposure phase except that now all of the peripheral locations are shown as blue spheres. One of the patterns presented in the exposure phase is presented in the center location. With the presentation of this pattern, the participant is required to select the peripheral location where an identical pattern is hidden beneath the blue sphere. This process continues until the correct location of each pattern is

found. Finding the correct location for all patterns in the set is defined as a learning trial. There are six learning trials (a single trial delayed recall condition will be done after a 30-minute delay). The software records each move as an error or as a correct move.

This assessment takes approximately 7 minutes to perform.

Groton Maze Learning Test (Executive Function)

The Groton Maze Learning Test (GMLT) measures executive function using a maze learning paradigm. A 10 x 10 grid of tiles is presented to the participant on the screen. A 28-step pathway is hidden among these tiles. A blue tile indicates the start and a tile with red circles indicates the finish. The participant must move one step at a time from the start toward the end by touching a tile next to their current location. If the correct move is made a green checkmark appears and if the move is incorrect a red cross is revealed. Once completed, they are returned to the start location to repeat the test and must try to remember the pathway they have just completed. The software records the total number of errors made in attempting to learn the same hidden pathway on 5 consecutive trials during a single session.

This assessment takes approximately 7 minutes to perform.

8.1.5.11 Karolinska Sleepiness Scale (KSS)

The Karolinska Sleepiness Scale (KSS; Akersted and Gillberg 1990, Baulk et al 2001) will be completed as part of the safety assessments (see Section 8.2.7). The KSS measures the subjective level of sleepiness at a particular time during the day. On this scale, participants (or support persons for adolescents aged 15 to 17 years and for low-functioning participants) indicate which level best reflects the psycho-physical state experienced in the last 5 minutes. The KSS is a 9-point scale (1 = extremely alert, 9 = very sleepy, great effort to keep awake, fighting sleep).

This assessment takes approximately 5 minutes to perform.

8.1.5.12 Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS; Johns 1991, Johns 1992) will be completed as part of the safety assessments (see Section 8.2.7). The ESS is a brief, self-administered eight-item questionnaire that measures daytime sleepiness in adults. Participant will be asked to rate on a scale of 0-3 the chances that, “over the past month” and “since last visit”, he/she would have dozed in eight specific situations that are commonly met in daily life (0 = would never doze; 3 = high chance of dozing). Thus, the participant is asked to characterize, retrospectively, part of his usual behavior in a variety of situations that are more or less soporific. The ESS score is the sum of eight item-scores and can range from 0 to 24.

This assessment takes approximately 5 minutes to perform.

8.1.5.13 ESS for Children and Adolescents (ESS-CHAD)

The Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD; Johns 2015) will be completed as part of the safety assessments (see Section 8.2.7). The ESS-CHAD is a brief, support person-administered eight-item questionnaire that measures daytime sleepiness in children and adolescents. Support persons of adolescents and participants with an IQ score <70 will be asked to rate on a scale of 0-3 the chances that, "Over the past month," and “since last visit”, “your child” would have dozed in eight specific situations that are commonly met in daily life (0 = would never doze; 3 = high chance of dozing). Thus, the support person is asked to characterize, retrospectively, part of his usual behavior in a variety of situations that are more or less soporific. The ESS score is the sum of eight item-scores and can range from 0 to 24.

This assessment takes approximately 5 minutes to perform.

8.1.5.14 Sudden Onset of Sleep Questionnaire

The Sudden Onset of Sleep Questionnaire has been developed by the Sponsor for this study and will be completed as part of the safety assessments (see Section 8.2.7). Each participant (or support person for adolescents aged 15 to 17 years and for low-functioning participants) will be asked to answer a series of up to 8 questions to assess the occurrence of daytime somnolence, its suddenness (level of awareness), frequency and circumstances in which the episode(s) took place, impact on work/daily activities/ social life, if worried by episode and ease of waking up (see Appendix 2 for reporting of AEs). This questionnaire will be administered as an interview.

This assessment takes approximately 5 minutes to perform.

8.1.5.15 Patient-Reported Outcomes Measurements Information System (PROMIS) Sleep Disturbance Questionnaire Short Form

The Patient-Reported Outcomes Measurements Information System (PROMIS) Sleep Disturbance Short Form (Yu Lan et al 2011, Buysse et al 2010) assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. This includes perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. This questionnaire assesses sleep disturbance over the past seven days.

The following versions of the Sleep Disturbance short form (8 items) will be implemented in this study: adult self-report (ages 18+, high-functioning), pediatric self-report (adolescents aged 15 to -17 years, high-functioning). In addition, proxy forms completed by the support person will be used for all adolescents, as well as low-functioning adults.

This assessment takes approximately 5 minutes to perform.

8.1.5.16 Patient-Reported Outcomes Measurements Information System (PROMIS) Sleep-Related Impairment Questionnaire Short Form

The PROMIS Sleep-Related Impairment Short Form (Buysse et al 2010) focuses on self-reported perceptions of waking alertness, sleepiness, and function within the context of overall sleep-wake function. This questionnaire assesses sleep-related impairment over the past seven days.

The following versions of the PROMIS Sleep-Related Impairment Short Form (8 items) will be implemented in this study: adult self-report (ages 18+, high-functioning), pediatric self-report (ages 15 to 17, high-functioning). In addition, proxy forms completed by the support person will be used for all adolescents, as well as low-functioning adults.

This assessment takes approximately 5 minutes to perform.

8.1.5.17 Entry and Exit Questions

Support persons will be asked a set of entry questions at baseline about their expectations regarding the study drug and about the skills or behaviors of the study participant they would like most to see improve.

As a follow-up, at the Week 12 visit or Early Termination visit, support persons will be asked to report if they observed any changes in the skills or behaviors of the study participant during the study, as well as some feedback on the study drug.

Both entry and exit questions will be answered on an electronic device.

The entry and exit questions will take about 5 minutes to complete.

8.1.6 Other Assessments

For PD biomarker assessments see Section 8.7.1.

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious adverse events of special interest (NSAESI); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

8.2.1 Medical History, Demographic Data, and Support Person Information

Medical history includes clinically significant diseases experienced up to screening plus for the previous 5 years: developmental history, date of ASD diagnosis, psychiatric history, smoking habits and history, use of alcohol and drugs of abuse, medical interventions (e.g., immunizations/vaccines, pharmacological therapies, non-pharmacological therapies, and surgeries.

Demographic data will include age, sex, and participant-reported race/ethnicity as well as applicable information about residential setting, school or employment status, 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 support person who will oversee the participant's adherence with protocol-specified procedures, and report on the participant's status. This will include, for example, their relationship to the participant, time spent with the participant, whether they live in the same residence, level of education and school, or employment status.

In addition, information about ASD and other psychiatric or neurological conditions in the study participant's family will be recorded in order to explore potential familial patterns and examine links to genetic information such as variants of pathways related to ASD or metabolic enzymes that alter efficacy or safety outcomes (see Section 8.7.2).

Some of this information will be forwarded, along with other pertinent information, as part of the screening process with the EAF (Section 8.11.1).

8.2.2 Physical Examinations

A complete physical examination will be performed at the times indicated in the SoA (Section 1.3) and include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal in addition to head, eyes, ears, nose, throat, neck and lymph nodes systems. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Height and weight will be recorded at the times indicated in the SoA (Section 1.3) and used to calculate the BMI.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.3 Vital Signs

Vital signs will include temperature (tympanic), SBP and DBP, and pulse rate. They will be taken before blood collection and measured in a supine position after at least 5 minutes of rest. At some timepoints, BP will also be measured in two positions (once supine and once, 3 minutes later, standing) for orthostatic changes. At visits with dosing, vital signs and orthostatic changes will be measured pre-dose and postdose (for frequency see SoA (Section 1.3).

Blood pressure and pulse measurements will be assessed obtained in a quiet room at a comfortable temperature, with the participant's arm unconstrained by clothing or other material and using a completely automated device with a digital readout throughout the study. Manual techniques will be used only if an automated device is not available. When possible, the same arm should be used for all blood pressure measurements.

8.2.4 Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the HR and measures QRS complex, PR, QT, and QTc intervals.

The three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 5 minutes.

To minimize variability, it is important that participants be in a resting position for at least 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in HR. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to meals and any scheduled vital sign measurements and blood draws.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

If any values at or beyond the protocol-defined parameters are detected from the machine reading, an expedited review by the central vendor should be requested to confirm the reading.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant’s permanent study file at the site.

The recordings will be electronically transferred to a central ECG analysis vendor. The following parameters will be obtained from the digital recordings: heart rate, QRS duration, PQ (PR), RR and QT intervals (QTcB (Bazett's correction) and QTcF (Fridericia's correction) as well as information on T-wave and U-wave. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF or may be sent electronically. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including HR, QRS duration, and PR, and QT intervals, will be recorded on the eCRF or loaded electronically. QTcF, QTcB and RR interval will be calculated automatically and recorded on the eCRF or loaded automatically. T-wave information will be captured as normal or abnormal and U-wave information will be captured in two categories: absent/normal or abnormal.

8.2.5 Clinical Safety Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in Appendix 4 and these assessments must be conducted in accordance with the separate laboratory manual and the SoA (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory assessments performed at the local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification) then, the results must be recorded in the eCRF.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety.

Where the clinical significance of abnormal laboratory results at screening are considered uncertain, screening laboratory tests may be repeated before randomization to confirm eligibility.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If there is an alternative explanation for a positive blood test for drugs of abuse (e.g., previous occasional intake of a medication or food containing for example, codeine, benzodiazepines or opiates) the test could be repeated to confirm washout. Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory.

8.2.6 Suicidal Risk Monitoring

A baseline assessment of suicidal ideation will be performed and treatment-emergent suicidal ideation and behavior during the study will be monitored using the Columbia Suicide Severity Rating Scale (C-SSRS) forms “At Baseline” and “Since Last Visit” at the timepoints indicated in the SoA (Section 1.3). C-SSRS assessments will be completed by a certified clinician.

Participants being treated with RO7017773 or placebo should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing study treatment in participants who experience signs of suicidal ideation or behavior.

Families and support persons of participants being treated with RO7017773 or placebo should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator.

8.2.7 Cognitive Assessments and Measures of Somnolence or Sudden Onset of Sleep

As part of the safety assessments, support persons will complete the PedsQL™ Cognitive Functioning Scale and participants will be asked to perform a number of cognitive assessments designed to measure specific areas of cognition. The description of these assessments is included in Section 8.1.5.9 (PedsQL™ Cognitive Functioning Scale) and Section 8.1.5.10(Neurocognitive Battery). The KSS, ESS or ESS-CHAD scales, and the Sudden Onset of Sleep Questionnaire will be used to assess somnolence and sudden onset of sleep. These scales and questionnaires are described in Section 8.1.5.11, Section 8.1.5.12, Section 8.1.5.13, and Section 8.1.5.14.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The NSAESI and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Section 8.3.6 and Section 8.3.7.

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on AEs at each participant's contact. All AEs, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study treatment**, only SAEs caused by a protocol-mandated intervention should be reported. Any other AEs should not be reported.

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until the last follow-up visit (approximately 42 days after the last dosing; see SoA in Section 1.3).

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period after the last follow-up visit (approximately 42 days after the last dosing; see SoA in Section 1.3).

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation time-points.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow up each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or study-related procedures until a final outcome can be reported. If a participant discontinues from the study early (as described in Section 4.1.2 and Section 7), all AEs should be followed up until they are resolved as long as the participant has not withdrawn consent..

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the participant'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.

All pregnancies reported during the study should be followed up until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

8.3.3.2 Sponsor Follow-Up

For SAEs, NSAESI, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, 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 event.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, Investigators, IRB and EC, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours a day 7 days a week. Details will be available separately.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 28 days after the final dose of study treatment.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Non-Serious Adverse Events of Special Interest

Non-serious adverse events of special interest (NSAESI) 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 Appendix 2 for reporting instructions).

NSAESIs for this study include the following:

- Hypersomnia, somnolence, depressed level of consciousness or lethargy of intensity other than mild (i.e., > Grade 1 according to the Common Terminology Criteria for Adverse Events [CTCAE]; see Appendix 9)
- Sudden onset of sleep (see Appendix 9 for determining if an event should be classified as sudden onset sleep versus somnolence or both and its severity)
- Paradoxical effects (see Section 8.3.7)
- Rebound and/or withdrawal symptoms after drug discontinuation (e.g., insomnia, anxiety, distress, weight loss, dizziness, night sweats, shakes, muscle twitches, indigestion, diarrhea, and photophobia)
- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3, Section 6
- Confirmed QTcF (average of triplicate values) >480 msec based on central ECG reading
- Confirmed QTcF (average of triplicate values) change from baseline >60 msec based on central ECG reading
- Gastrointestinal events other than mild (see Appendix 2, Section 3.1); preferred term examples for gastrointestinal events are provided in Appendix 10)
- Suspected transmission of an infectious agent by the study treatment, 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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.3.7 Management of Specific Adverse Events

Treatment of specific AEs will be considered on a case-by-case basis according to local standard of care.

Several measures are taken to ensure the safety of participants participating in this study. Eligibility criteria have been designed to exclude participants at potentially higher risk for toxicities. Participants will undergo safety monitoring during the study. In addition, guidelines for managing AEs, including criteria for treatment interruption or discontinuation, are provided in the following sections.

Participants should not engage in hazardous activities while taking study medication (see Section 5.3).

8.3.7.1 Potential Risks Associated with RO7017773

[redacted]

The other risks described below, e.g., neuropsychiatric effects, withdrawal symptoms, paradoxical reactions, reflect the effects observed with the non-selective GABA-A positive allosteric modulators class or with CNS-active compounds (suicidality).

[redacted]

Neuropsychiatric Effects

As for other psychotropic substances targeting the CNS, participants will be closely monitored for signs and symptoms of neuropsychiatric changes (e.g., agitation and mood changes) including routine monitoring of the major depressive disorders and using the C-SSRS (see Section 8.2.6).

Suicidality

RO7017773 is considered to be a CNS-active study treatment. There has been some concern that some CNS-active study treatments may be associated with an increased risk of suicidal ideation or behavior when given to some participants. To date, clinical experience in healthy participants does not point to any suicidality liability of RO7017773. However, monitoring for suicidality (see C-SSRS in Section 8.2.6) is mandatory in clinical studies of CNS active molecules and will be implemented with the C-SSRS. The Investigator is asked to assess individually appropriate next steps if a suicidality alert arises.

Withdrawal Symptoms

At present, neither nonclinical nor clinical observations point to a liability of withdrawal symptoms after stopping RO7017773 treatment. However, because of the effect of RO7017773 on the GABAergic system, participants will be evaluated for potential rebound and/or withdrawal effects following the cessation of treatment (see Table 10). AE monitoring is continued for 6 weeks after the last dose, which is considered appropriate in the context of a half-life of less than approximately 20 hours. Should withdrawal symptoms (sleep disturbance, irritability, increased tension and anxiety, hand tremor, shaking, sweating, difficulty with concentration) occur, symptomatic treatment is recommended. Reintroducing RO7017773 is not foreseen.

Occurrence of withdrawal seizures has been sometimes described in patients after benzodiazepine discontinuation, usually after long periods of treatment and at high doses (Tolbert et al 2014).

Paradoxical Reactions to RO7017773

As the sensitivity of individuals to PAMs of the $GABA_A$ receptor may differ, the occurrence of paradoxical reactions characterized by increased talkativeness, emotional release, excitement, and excessive movement are rarely described with benzodiazepine use (Mancuso et al 2004) but cannot be excluded following administration of RO7017773.

Cardiovascular effects

Changes in Blood Pressure

Measurement of vital signs and ECG assessment of the HR will be performed throughout the study. Additional assessments of vital signs might be considered by the Investigator.

Changes in QTcF Interval

Because patients with ASD may be receiving atypical antipsychotics that may prolong QTc, ECG abnormalities will be monitored at the initiation of RO7017773 treatment to address this risk.

Initiation or Change of Drug Regimen that is Known to Prolong QTc

An additional ECG should be obtained in triplicate from participants requiring a new treatment or requiring a change of treatment regimen with a medication known to prolong the QTc (e.g., to treat an AE) at the earliest convenience after start/change of this treatment. A list of drugs known to prolong QTc is provided in Appendix 8). In case of questions, the Investigator should contact the Sponsor (Medical Monitor or designee).

[redacted]

8.3.7.2 Guidelines for Managing Specific Events

Guidelines for managing specific events are provided in Table 10.

In any case the site should evaluate the participant as soon as possible (e.g., plan an unscheduled visit if required). The participant should be evaluated by the Investigator and a psychiatrist or other specialist as applicable (in case not the same person). The Investigator should then contact the Sponsor's Medical Monitor to discuss further steps

(e.g., consider switching the time of study drug administration from morning to evening, pause dosing and consider restarting after resolution of symptoms). If a participant discontinues from the study early (as described in Section 4.1.2 and Section 7), all specific events should be followed up until they are resolved as long as consent has not been withdrawn.

Table 10 Guidelines for Managing Specific Events

Type of Risk	Risk Mitigation
CNS effects • Daytime somnolence, sudden onset of sleep, dizziness	• If daytime somnolence or sudden onset of sleep occurs during a site visit within 1 hour postdose, or anytime thereafter, the Investigator will monitor vital signs and orthostatic changes hourly for 3 hours and more frequently if clinically warranted, perform ECG in triplicate, and record the number of minutes asleep for each event of falling asleep. • Investigators will instruct the participants and their support persons to contact the site immediately if daytime somnolence (other than mild) or sudden onset of sleep occurs outside of the specific site visits and to take the appropriate safety precautions with ambulation and driving (if applicable). In case of mild episodes of somnolence or daytime somnolence, switching dosing from morning to evening administration should be considered after discussion with the Sponsor's Medical Monitor. • In case of recurrent, sustained, or medically relevant episodes of hypersomnia, daytime somnolence, lethargy, sudden onset of sleep, decreased level of alertness, or dizziness, discontinuation of dosing and withdrawal of the participant should be considered.
Psychiatric effects • Mood disorders, major depression disorders • Agitation, irritability emotional release, excitement, and excessive movement	• Severe, pause dosing • Assess if signs and symptoms evoke paradoxical reactions, stop dosing, consider symptomatic treatment
Suicidal risk	• In case of treatment-emergent suicidal risks, complete the C-SSRS and consider further evaluation and clinical management (e.g., immediate referral to mental health services and patient safety precautions)

Table 10 Guidelines for Managing Specific Events (cont.)

Type of Risk	Risk Mitigation
Withdrawal/rebound effects	• Depending on the severity, consider surveillance and symptomatic treatment (e.g., midazolam, diazepam, melatonin, and trazodone) • In case of emerging symptoms of rebound and/or withdrawal effects of the study drug during the follow-up period after end of treatment at Week 12, treatment with benzodiazepines is allowed (if possible after discussion with the Sponsor). • Seizures; Handling of seizures should follow the recommendation by the International League against Epilepsy (https://journals.sagepub.com/doi/10.5698/1535-7597-16.1.48): – In case of participants with a first seizure, the local emergency doctor should be called; the diagnostic workup as well as the treatment will depend on the type and duration of the seizure. – In case of participants with known seizures, the emergency medication (typically, intramuscular midazolam, intravenous (IV) lorazepam, or IV diazepam) should be given after 3 to 5 minutes (as per local recommendation).
Paradoxical reactions	• Depending upon severity, consider symptomatic treatment; if necessary take the advice of an emergency physician (treatment option: e.g., blood pressure management, physostigmine, flumazenil, and haloperidol) • If a participant experiences a paradoxical reaction, anxiety, or mood agitation, treatment must be paused and can be restarted only after discussion with the Sponsor.
Overdose with exacerbated CNS effects	• In cases of exacerbated symptoms of sedation, coma, or respiratory depression, consult an emergency physician and apply symptomatic treatment (e.g., blood pressure and airway management, flumazenil).
QTc Prolongation	• QTcF (average of triplicate values) >480 msec or a change from baseline of >60 ms (when confirmed in repeat measurement within 30 minutes and based on central reading): stop dosing (see also stopping rules in Section 4.1.2) • If the QTcF does not normalize after interruption of the study drug and a washout period of 1 week, the participant should receive appropriate emergent treatment and be referred to a cardiologist for evaluation.

Table 10 Guidelines for Managing Specific Events (cont.)

Type of Risk	Risk Mitigation
Liver effects (see also stopping rules)	• Confirmed ALT/AST of >3-fold the ULN and associated with an increase in bilirubin (>2-fold the ULN): stop dosing, repeat testing within 48 to 72 hours and repeat two to three times per week until resolution, consider advice from a hepatologist. • Further evaluation should include serum sample and additional laboratory tests (e.g., GLDH, viral serology, such as hepatitis B, hepatitis C, Epstein-Barr virus, cytomegaly virus and herpes simplex virus).
Gastro-intestinal disorders, (e.g. nausea, vomiting, abdominal pain)	• In cases of gastro-intestinal events of nausea and /or vomiting, apply symptomatic treatment. In case of gastro-intestinal events of moderate (or worse) severity, contact the Sponsor's Medical Monitor to discuss further steps.
Hypersensitivity	• In case of suspected hypersensitivity to RO7017773, stop dosing, take appropriate action including symptomatic treatment and contact Sponsor's Medical Monitor.

8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental administration of a drug in a quantity that is higher than the assigned dose. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

Decisions regarding dose-interruptions or modifications (if applicable) will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant (see Table 10).

RO7017773 is a selective $GABA_A$ α5 PAM which at high doses [redacted] loses its selectivity for the $GABA_A$ α5 receptor and may bind to other GABA receptors in the brain. RO7017773 overdose is expected to result in excessive sedation or somnolence, and possibly coma and respiratory depression.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.

3. Obtain, if possible, a blood sample for PK analysis within 24 hours from the date of the final dose of study treatment, if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF.
5. In case of overdose with exacerbated CNS effects, refer to guidelines for man gauging overdose with exacerbated CNS effects in Table 10.

Previous PK samples collected at the time of the incorrect administration of study treatment may be used to further evaluate overdose.

8.5 PHARMACOKINETICS

Blood samples for the determination of plasma concentrations of RO7017773 will be collected as outlined in the SoA (see Section 1.3. *Note: On visits Day 1 and Day 14, the study drug should be taken with breakfast or some food such that* t_{max} *is reached after approximately 2 hours*). *Following review of the second interim analysis, sampling on Day 1 may be reduced for adolescents to be similar to that for high- and low-functioning adults. This will be confirmed as part of the IMC + SOC review of PK data from adolescents.* Plasma RO7017773 concentrations will be measured by a specific and validated LC-MS/MS method. Topical application of local anesthetic is permitted if necessary for blood sampling. Home nursing services may be provided, if feasible to collect blood samples at the participant's household.

If required, remaining PK samples may also be used for assay development/validation (e.g., for metabolites and measurement of exploratory biomarkers).

The PK samples will be destroyed within 2 years after the date of final CSR. Details on sampling procedures, sample storage and shipment are given in the Sample Handling Manual.

For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.9).

Drug concentration information that would unblind the study, will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of timepoints for any planned study assessments must be documented and approved by the relevant study team member and archived in the Sponsor and site study files. This will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6 IMMUNOGENICITY ASSESSMENTS

Immunogenicity will not be evaluated in this study.

8.7 BIOMARKER ANALYSES

The rationale for using these specific tests is provided in Section 4.2.3.

8.7.1 Biomarkers

8.7.1.1 Digital Biomarkers

At the pre-baseline visit, the support person and the participant will be provided with a study smartphone and smartwatch, a “sleep mat”, detailed instructions and training on how to use the technology, *and, optionally*, small Bluetooth transmitters (“beacons”). The number of “room beacons” should be based on the number of rooms within the participant’s home and their sociability level as reported by the support person and participant, and at least one “more social” and one “less social” room beacon must be dispensed. The support person and participant will be instructed to place one “room beacon” in each separate room of the participant’s home (as appropriate) based on their sociability level (“more social” or “less social”). Regarding the “people beacons”, at least one will be dispensed to the support person, or a number to match the number of people living with the participant and that are eligible to carry a beacon. The support person and participant will be instructed to distribute the “people beacons” to each member of the household, where appropriate. The people beacons should be worn by the household members whenever they are at home. Any complementary information related to the dispensing of beacons can be reported in the “Dispense” eCRF’s form in the “comments” field. The beacons transmit a regular Bluetooth signal that is recorded by the watch, allowing for an estimation of the proximity of the beacon. The study phone and watch will have applications pre-installed, that include a collection of digital biomarker assessments, comprising surveys and active tasks, for the support person and participant to complete. The applications will collect:

1) Smartphone data through user interaction (Active Tasks)

   Participants will be assessed with *three* active tasks within the smartphone app. *In total the* active *tasks* will last *on average 5* minutes. The tasks will assess spatial working memory, emotion recognition as well as social and communication deficits. Once a week, support persons will be asked to record a conversation with the participant that is at least 5 minutes long to assess communication deficits. When not in use, the phone should be left in the participant’s living room on charge whenever possible. Throughout the day the phone will measure the volume of noise in the environment and the time that people spend speaking. The raw audio recordings (and so actual words spoken) will not be uploaded from the phone and will be automatically deleted from the phone. For more details on the audio recordings please see Appendix 11.

2) Smartphone and smartwatch data without user interaction (Passive Monitoring)

   The participant will be asked to wear a smartwatch each day for the continuous capture of behavioral and physiological data related to core and associated symptoms of ASD ('passive monitoring'), including (a) body movement to characterize repetitive body movements, (b) heart-rate parameters as biomarkers of anxiety and stress, (c) dereferenced geolocation and time information to characterize social behavior when outdoors, *and* (d) level and quality of background sound to characterize social interactions (recorded on smartphone).

   The people beacons also include a button that should be pressed by the support person when they observe the participant performing a repetitive movement. This "tagging" of repetitive movements can also be performed in the smartphone app. To avoid over-burden, tagging needs not be done for every observed repetitive movement. However, for a successful assessment a substantial number of events (e.g., a few each day) need to be tagged. Furthermore, the support person should tag all repetitive movements for a certain period of time (at least 2 hours) on a day of their own choice, i.e. to do "dense" tagging.

3) Participant and Study-Partner Reported Outcomes on smartphone (Surveys)

   Once per month questions on HRQoL (EuroQol 5-Dimension, 5-Level Questionnaire [EQ-5D-5L]) will be asked.

In addition, a sleep mat that will be placed by the support person under the participant's mattress and contains a sensor to detect *body movement*, breathing and heart-rate signals that will be used to collect data on sleep behavior.

The ability of the participant to complete the active tasks will be assessed by the clinician at the pre-baseline visit and if any of the active tasks are not suitable for the participant, they will be deactivated on the study smartphone. Participants and support persons will have the opportunity to ask any questions they may have. During the study, at scheduled phone contact and site visits, site personnel will follow-up on the participant's progress. Adherence and technical status of the technology will be checked throughout the study, and the participant and support person will receive daily reminders to complete the active tasks and surveys, which may include calls from the site. The technology must be returned to the clinic at the end of the study and upon early termination. At those times, both the participant and the support person will be asked to complete satisfaction surveys on their experience using the technology during the study.

Full details on the type of data captured and the methods used to ensure participant privacy are provided in Appendix 11.

8.7.1.2 Hair Biomarkers

The exposome assay will provide 4- to 6-hour molecular measurements of physiological metabolites, environmental chemicals, and essential elements such as zinc and copper. The metabolic and biochemical dynamics of the participants, i.e., temporal changes in the levels of the different factors that are assessed, will be mapped from before the start of study drug administration throughout the treatment and follow-up periods to identify which molecular pathways show a sustained response to the study drug (see SoA, Section 1.3). In addition to monitoring the temporal exposome of the participants at the molecular level, the hair assay may also assess the levels of RO7017773 and its metabolites to provide further information on the relationship of potential changes in the exposome with RO7017773 administration. Lastly, the data generated by the hair assay will be used to undertake molecular phenotyping to identify participant subgroups who respond differently to the study treatment. Optional hair samples from support persons who provide consent will serve as a control.

8.7.1.3 Pharmacodynamic Biomarkers: Assessments of Neurophysiological Effects

The PD biomarker assessments comprise resting state EEG and SPV (measured by means of EOG recorded during an oculomotor task). These assessments will be performed at the timepoints specified in the SoA (Section 1.3). Resting state EEG will be acquired in alternating 1 min blocks of eyes open and eyes closed while participants sit relaxed, following the recommendations of the International Pharmaco-EEG Society (Jobert et al 2012). Resting state data will be processed off-line to derive the beta power (12 to 30 Hz). During the oculomotor task, participants will be instructed to look at and follow a target stimulus on the screen, which switches horizontally from the screen center to either side at fixed amplitudes. Participants' head movements will be reduced by means of a chin rest. The system will be initially calibrated to establish the conversion between EOG signals and eye movement amplitude. EOG data will be analyzed off-line to derive saccadic peak velocities.

8.7.1.4 Response Biomarkers: Eye-Tracking and Task EEG Biomarkers

Eye-tracking and task EEG biomarkers will be acquired twice: before dosing and at the end of treatment (see SoA in Section 1.3).

In the eye-tracking assessments, participants will be presented several static and dynamic visual stimuli while the eye-tracking system estimates their gaze position and pupil size. The visual stimuli include social (faces, people, activities, biological motion, etc.) and non-social elements (toys, objects, background furniture, etc.). Derived parameters will include time spent looking at specific stimuli type and image and video scanning patterns. Additionally, participants' pupil constriction during pupillary light reflex will be measured.

During the task EEG assessments, participants will perform tasks with visual stimulation. This will *consist of a* "Face ERP" task, where they look at images of upright faces, inverted faces, and houses. Derived parameters for analyses will include event related potential component amplitudes and latencies.

The response biomarker assessments will be performed after the PD biomarker assessments (see Section 8.7.1.3) and are ordered by priority on the recording setup. In case low-functioning participants are not able to complete the full set of response biomarkers (e.g., because of agitation or inability to wear the EEG cap for the duration of the entire task battery), the remaining tasks may be skipped.

8.7.2 Genetic and Genomic Analyses

8.7.2.1 Clinical Genotyping

In this study, genetic analyses will be performed to possibly identify subgroups of individuals who benefit from RO7017773.

A mandatory whole blood sample will be taken from every participant for DNA extraction (see SoA in Section 1.3 and Section 8.8.1). The DNA may be used for, but analysis is not limited to:

- Genetic variants of pathways related to ASD, including but not limited to genes related to disease status, drug target, and treatment response.
- Genetic variants of CYPs, transporters or receptors which might affect the metabolism, PK, PD, or safety of RO7017773.

Data arising from all biosamples will be subject to the same confidentiality as the rest of the study (see Appendix 1).

8.7.2.2 Whole Genome/Exome/Targeted DNA Analysis

The sample collected for DNA extraction (see Section 8.8.1) includes, but is not limited to, genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

Given the complexity and exploratory nature of these analyses, genomic data and analyses will not be shared with Investigators or study participants unless required by law. Participants will not be identified by name or any other personally identifying information. Data arising from all biosamples including samples for analyses of inherited DNA will be subject to the confidentiality standards described in the sample documentation.

8.7.3 Overview of the Research Biosample Repository

The Roche RBR is a centrally administered group of facilities for the long-term storage of human biologic samples, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of the RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional RBR. Collected RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, AEs, or progressive disease.
- To identify safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation.
- To increase knowledge and understanding of disease biology and drug safety.
- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

8.8 BIOMARKER SAMPLES

8.8.1 Mandatory Samples

The following samples are required and will be collected from all participants in this study:

- Whole blood sample for DNA extraction (see Section 8.7.2)
- Hair samples for exposome analysis (see Section 8.7.1.2)
    - *Note: No hair samples will be collected from study participants with no or insufficient hair.*

A mandatory whole blood sample will be taken for DNA extraction to support clinical genotyping from every participant at any convenient time between Day 1 and follow-up

visit. In addition, hair samples for exposome analysis will be collected at the timepoints specified in the SoA (see Section 1.3).

Clinical genotyping samples and derived analytical material will be destroyed within 5 years following completion of the CSR. Hair samples for exposome analysis will be destroyed within 2 years following completion of the CSR. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual and instructions.

For participants who consent to RBR, leftover blood and hair samples will be transferred to RBR (see Section 8.9).

8.8.2 Optional Samples

Optional hair samples will be collected from support persons who provide consent on the applicable ICF at the timepoints specified in the SoA (see Section 1.3). These optional samples will serve as a control to assess the potential contribution of shared environmental factors in the exposome analysis (see Section 8.8.1).

8.9 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.9.1 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to ASD and related disorders and drug safety:

- Leftover PK samples (see Section 8.5)
- Leftover genetic sample (see Section 8.8.1)
- Additional whole blood sample for RBR on Day 1 predose and at Week 12 or Early Termination visit (see SoA in Section 1.3)
- Leftover hair samples of the study participants (see Section 8.8.1)

The sample collected for DNA extraction include, but is not limited to, genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

The hair samples may likewise be sent to other laboratories and analyzed with exposomic methods. Biochemical assays of the hair samples will allow molecular phenotyping, which is not possible with blood analysis alone. These data will interface with other datasets, including genomics data, to support the identification of potential new targets and pathways.

Participants will not be identified by name or any other personally identifying information. Data generated from RBR samples will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For all samples, dates of consent and sample collection should be recorded on the associated RBR page of the eCRF. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

RBR samples will be stored and used until no longer needed. The RBR storage period will be in accordance with the IRB/EC‑approved ICF and applicable laws (e.g., Health Authority requirements).

The repository samples will be subject to the confidentiality standards (as described under Confidentiality and in Appendix 1).

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.11 TIMING OF STUDY ASSESSMENTS

8.11.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for enrolled participant and for participants who are not subsequently enrolled will be maintained at the study site.

All screening assessments (related to entry criteria), must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Screening and pretreatment assessments (i.e., assessments at the pre-baseline and baseline visits) will be performed at the timepoints indicated in the SoA (see Section 1.3); however, in case of unexpected delays due to logistical or technical reasons (e.g., sickness of support persons or raters), the screening or pre-treatment period (see Figure 1) may be extended to up to 2 additional weeks. Beyond these 2 weeks, the participant is considered a screen failure, but can be re-screened (see Section 5.4).

Once all inclusion and exclusion criteria are met, the EAF (see Sections 1.3 and 8.2.1) is sent to the external vendor as part of the screening process, ideally before the pre-baseline visit. The Principal Investigator will decide whether a participant will be enrolled and may consult with the Sponsor (Medical Monitor or designee) for advice or clarification of any eligibility criteria.

The Principal Investigators are highly encouraged to use the voluntary eligibility consultation offered by the external vendor to ensure meeting all eligibility criteria and avoid protocol deviations related to participant eligibility.

For a participant to enter the randomized, double-blind treatment period the following criteria must be fulfilled:

- No significant new or worsening psychiatric or medical illness since screening that in the opinion of the Investigator would interfere with the participant's ability to participate in the study.
- No change in medications since screening.

8.11.2 Assessments during Treatment

Under no circumstances will participants who enroll in this study and have completed treatment as specified be permitted to be allocated a new randomization number and re-enroll in the study.

All assessments must be performed as per SoA (see Section 1.3). The recommended order of assessments to be performed at the clinic will be defined in a separate document. The order of assessments may be adapted to allow efficient administration of all assessments at the site with the exception of assessments that have to be done at a specific time before or after taking the study drug as per SoA (see Section 1.3). The order of assessments that have to be taken at home is predefined on the electronic device for each participant (see Section 8.7.1.1). The site will contact the participant or support person over the phone to assess for any clinically significant symptoms and/or new medication, to ensure compliance to the study drug and digital biomarker assessments as well as to administer questionnaires/scales/tests when appropriate as per SoA (see Section 1.3).

8.11.3 Assessments at Follow Up /Early Termination Visit

Participants who complete the 12-week study treatment period will be asked to return to the clinic *approximately 2 weeks and 6 weeks* after the last dose of study treatment for safety follow-up visits (see Section 1.3).

Assessments at the follow-up/early termination visits will be performed as indicated in the SoA (see Section 1.3). After the study completion/early termination visit, AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

If participants discontinue from the study early (as described in Section 4.1.2 and Section 7), all efforts should be made to ask participants to return to the clinic for an early termination visit. All AEs should be followed up until they are resolved and additional unscheduled safety assessments should be performed at Investigator's discretion after discussion with the Medical Monitor if required.

8.11.4 Assessments at Unscheduled Visits

Unscheduled visits will be performed for safety reasons (e.g., for repetition of safety laboratory sampling). If due to a safety-related event a participant is unable to physically go to the site for an unscheduled visit, blood and urine samples may be collected by the home nurse services.

The unscheduled visit should be used to collect all assessments that are missing at that time.

If a COA (see Section 8.1.5) cannot be completed during the visit or for a scale, the total score (e.g., the composite scores for Vineland™-3) cannot be calculated with the available data, the scale should be repeated via the phone within the corresponding visit window or at an unscheduled visit as soon as possible (within the next 7 days).

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Because the nature of this Phase II study is purely hypothesis generating, no formal testing of a predefined null hypothesis is performed.

9.2 SAMPLE SIZE DETERMINATION

Approximately 105 participants with ASD randomized in a 1:1:1 ratio between two active dosing regimens and placebo need to be recruited in order to obtain evaluable data from approximately 84 participants after 12 weeks of treatment. Evaluable data from 84 ASD participants provides at least 80% power to detect a mean difference between baseline and 12-week follow-up of 4.5 points on a Vineland™-3 composite between any active treatment arm and the placebo arm with α = 0.10 error control (1-sided). The minimally

detectable difference in this cohort is 2.7 points. It is assumed that the standard deviation of the differences between baseline and 12 weeks follow up is 8.0 points, that 20% of participants will not provide evaluable data, and that the participants recruited will consist of at most 25% low-functioning participants, at most 25% female participants, and at most 75% adults. Because the purpose of this study is exploratory, no adjustment for comparison of multiple active doses to a single placebo arm is performed.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 11.

Table 11 Analysis Populations

Population	Description
Safety	All participants randomized to study treatment and who received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
Pharmacokinetic	All participants providing pharmacokinetic data will be included in the PK Population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
Efficacy	All participants who give informed consent, are randomized, and receive at least one dose of double-blind study medication. Data will be analyzed as per the actual treatment received.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics data such as baseline values of relevant scales, medical history including medications and treatments, support person status, educational status of participant and parents, etc. will be summarized by treatment, age cohort, and IQ cohort. Listings, summary tables of descriptive statistics, frequency tables, and corresponding graphs will be provided as appropriate.

9.4.2 Efficacy Analyses

The primary and secondary efficacy analyses will include all participants in the Efficacy Analysis Population (EAP).

The efficacy analyses detect the absolute change from baseline to follow-up. Mean change from baseline for the two active doses and placebo will be compared. An

analysis of covariance (ANCOVA) model will be used to compare treatment effects for the primary and continuous secondary efficacy endpoints on the overall population of adolescents and adults. The model will include dose as main effect and individual age and IQ, interaction of treatment versus age, interaction of treatment versus IQ, and baseline score as covariates. Treatment differences will be estimated together with their 90% confidence intervals as derived from the model and their associated p-values.

The ANCOVA model will be applied to change from baseline data y_{ij} of participants i, and treatment j $\in$ {placebo, low dose, high dose} as follows:

$$y\_ij=\mu+t\_j+a\_i+IQ\_i+t\_j*a\_i+t\_j*IQ\_i+BL\_i+\varepsilon\_ij$$

where μ gives the overall endpoint mean change, followed by the fixed effect (t) which models the effect of treatment, age (a), IQ, interaction terms, the endpoint baseline value (BL), and ε, which gives the overall error term with $N(0,\sigma_\varepsilon^2)$.

Primary Analysis

The primary efficacy analysis detects the mean change from baseline to 12 weeks of treatment as measured by the Vineland™-3 three-domain composite. The mean change from baseline of the two active doses and placebo will be compared.

Table 12 Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary Secondary Exploratory	ANCOVA

9.4.3 Safety Analyses

All safety analyses will be based on the safety analysis population.

Table 13 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by tabular summaries and individual listings with flagging of abnormal results.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries of raw values and change from baseline will be used, as appropriate.
ECG	ECG data will be presented by individual listings. In addition, tabular summaries of raw values and change from baseline will be used, as appropriate.
Concomitant medications	The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented in summary tables and listings.
C-SSRS, PedsQL™ Cognitive Functioning Scale, and cognitive assessments, KSS, ESS or ESS-CHAD, and Sudden Onset of Sleep Questionnaire	Data will be presented in summary tables and listings

9.4.4 Pharmacokinetic Analyses

For all participants, plasma concentrations of RO7017773 will be presented descriptively by dose.

Nonlinear mixed effects modeling may be used to analyze the sparse sampling dose versus concentration versus time data collected for RO7017773. The PK data collected in this study may be pooled with data from other clinical studies conducted with RO7017773. Population and individual PK parameters such as clearance and volume of distribution may be estimated, and the influence of various covariates such as age, gender, and body weight, on these parameters may be investigated. Secondary PK

parameters may be derived from the model as appropriate. The results of the analysis may be reported separately from the CSR.

The participant's exposure to RO7017773 may be assessed and correlated with selected efficacy, PD, biomarkers and safety parameters as appropriate.

9.4.5 Analysis of Clinical Outcome Assessments, and Exploratory Pharmacodynamic and Response Biomarker Analyses

All parameters will be presented by listings and descriptive summary statistics separately by group or cohorts.

9.4.6 Genotyping Analysis

The genotyping data may e.g., be used to derive ASD and GABA-related genetic scores for responder analyses.

9.5 INTERIM ANALYSES

Two interim safety analyses are planned for this study.

The first interim analysis of accumulated safety, tolerability and PK will be performed once approximately 18 high-functioning adults have completed 6 weeks of treatment. The aim of this analysis is to evaluate the safety, tolerability and PK in high-functioning adults before allowing the recruitment of the adolescents and low-functioning adult participants.

A second interim analysis of PK and accumulated safety and tolerability will be conducted once approximately 12 adolescents have completed 2 weeks of treatment. The aim of this analysis is to enable internal decisions to inform the design and dose selection for the adolescent participants and additional studies in the program.

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct such optional interim efficacy analyses and the timing of these analyses will be documented in the Sponsor's trial master file prior to the conduct of each interim analysis. The CSR will also document all interim analyses that occurred. All interim analyses will be performed and interpreted by members of the IMC, external experts (SOC), and appropriate senior management personnel. IMC and SOC members will be unblinded at the individual participant level, Sponsor senior management will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

The "IMC Agreement" will describe the planned interim analyses in detail.

9.6 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed. Data for study drug administration and concomitant medications will be listed. The number of participants who were enrolled, discontinued, and completed the study will be summarized and listed.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes Appendix 1 (for regulatory, ethical and study oversight considerations), Appendix 2 (for AE definitions, reporting) and Appendix 3 (Procedures of recording), Appendix 4 (Clinical laboratory tests), Appendix 5 (Contraceptive guidance and collection of pregnancy information), Appendix 6 (Examples of prohibited concomitant medications), Appendix 7 (Alcohol unit calculation – examples), Appendix 8 (List of Marketed Drugs Known to Prolong the QT Interval), Appendix 9 (Grading for Adverse Events of Special Interest with Regard to Somnolence, and Sleep), Appendix 10 (Preferred Term Examples for Gastrointestinal Adverse Events of Special Interest), and Appendix 11 (Supplementary Information for Digital Biomarkers).

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a 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 EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the participant (e.g., advertisements, diaries, etc.), 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 participant 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 (Section 2.3.1 of this Appendix 1).

The Investigator should follow the requirements for reporting all AEs to the Sponsor. 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.

1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Support person's 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. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed

consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant’s legally authorized representative.

In this study, support person specific information will be collected to evaluate support person burden requiring that a separate written informed consent be obtained from the support person. A separate, specific signature will be required to document a support person’s agreement to provide optional hair samples. Support persons who decline to participate will not provide a separate signature.

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

The ICFs should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved ICFs must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

If the ICFs are revised (through an amendment or an addendum) while a participant is participating in the study, the participant or a legally authorized representative may be re-consented by signing the most current version of the ICFs or the addendum, in accordance with applicable laws and IRB/EC policy). For any updated or revised ICFs, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study. The study team will provide guidance for which participants need to re-consent in the event of an update to the Consent form.

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

A participant who is re-screened is not required to sign another ICF if the re-screening occurs within 60 days from the previous ICF signature date.

Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their samples at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a participant who is participating in the Research, the participant's samples and data will continue to be used as part of the RBR.

For sites in the United States, each ICF may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for participant 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.

Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site

Withdrawal from the Research Biosample Repository

Participants who give consent to provide samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant's wishes using the RBR Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the study is closed. A participant's withdrawal from Study BP41316 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a

participant's withdrawal from the RBR does not constitute withdrawal from Study BP41316. Data already generated before time of withdrawal of consent to RBR will still be used.

1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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.

Confidentiality for Research Biosample Repository

Data generated from RBR samples must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR samples is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR sample analysis on individual participants will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or participants unless required by law.

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

Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the ICF. The Sponsor's monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

1.5. 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 one year after completion of the study (i.e., LPLV).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

2.1.2. Clinical Outcome Assessment Data

2.1.2.1 Electronic Clinical Outcome Assessment Data

An electronic clinical outcome assessment (eCOA) device will be used to capture COA data. The data will be transmitted electronically to a centralized database at the eCOA vendor. Entries should be reviewed for completeness during the clinic visit.

eCOA data will be collected using an electronic device provided by an eCOA vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

2.1.2.2 Remote Administration of Electronic Clinical Outcome Assessments

All caregiver- and patient-reported scales, forms, and interviews including the Vineland-3, CY-BOCS-ASD, and CGI assessments may be administered remotely *at the participants' home* if all requirements (see below) are fulfilled. This will reduce the duration of site visits and burden on participants and increase flexibility for both sites and study participants.

Detailed guidance will be provided to the study sites for remote administration of eCOA assessments by the eCOA vendor. Remote assessments should be scheduled within the corresponding visit window and can only be done if the participants have access to a location where privacy can be assured and distractions kept to a minimum. In addition, the participants need access to suitable hardware, software, and internet connections.

Remote caregiver- and patient-reported scales and forms will be performed using a secure screen-share connection with the site rater connecting to the regular electronic device provided by the eCOA vendor (see Section 2.1.2.1 above) *and the participants connecting remotely from their home or other suitable location. In case of unforeseen technical issues*, the assessments may be done via live videoconference or phone call with the site rater. Alternatively, devices for eCOA administration may be provided by the Sponsor for the duration of the study participation such that assessments can be performed directly on the device by the study participants and support persons. *If the Vineland-3 or CY-BOCS-ASD assessments are administered remotely at the participants' home, a live videoconference with the Central Rater will be used. Only in case of unforeseen technical issues the interview may be completed over the phone.*

For a given participant and/or support person, both on-site and remote assessments may be performed at individual study visits and for individual scales (i.e., they may choose the mode of administration freely). The mode of administration will be recorded on the eCOA device.

2.1.3. Source Data Records

Source documents (paper or electronic) are those in which participant 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, COAs (paper or eCOA), 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, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

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 below.

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

2.1.4. Use of Computerized Systems

When clinical observations are entered directly into an investigational 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.

2.1.5. Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study 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 destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor 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.

If Audio recordings have been used, they will be maintained on a secure server throughout the duration of the study and will be destroyed one retained for at least 15 years after study completion on approval by the Sponsor. No records may be destroyed during the retention period without the written approval of the Sponsor.

For countries where Ethics Committees or the Ministry of Health will not approve audio recording of participant interviews, review of the scale worksheets, submitted as part of the assessment source information, will be performed to verify accuracy of scoring and adherence to study conventions.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

Any substantial protocol amendments will be prepared by the Sponsor. Substantial 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 participants or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. 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.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

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.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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.

2.3.3. Dissemination of Clinical Study Data

A clinical study report containing the results of this study will be made available to anyone who requests a copy. A description of this clinical study and a summary of its results will be available at http://www.ClinicalTrials.gov.

2.3.4. Management of Study Quality

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to the first participant's entry into the study, the Sponsor will identify and evaluate potential risks associated with critical trial processes and data and will implement controls for the communication, review, and reporting of these risks. Details regarding the applied approach for the study will be provided in the integrated Risk Based Quality Management Plan.

Risk control includes the selection of risk-based parameters and establishing associated quality tolerance limits. Detection of deviations from defined quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the management and review of quality tolerance limits will be provided in a separate Quality Tolerance Limit Plan.

2.3.5. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' 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.

3. ADMINISTRATIVE STRUCTURE

The Sponsor of the study is F. Hoffmann-La Roche Ltd. The Sponsor is responsible for the study management, data management, statistical analysis and medical writing for the clinical study report.

This study uses an Internal Monitoring Committee (IMC) plus Scientific Oversight Committee (SOC). Details are provided in Section 4.1.3.

4. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants.

- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be:

- 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.

Events Meeting the AE Definition:

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) 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 treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- 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).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE unless the progression is unexpectedly accelerated and not in line with the natural history of the disease. If the “Lack of efficacy” would not require safety reporting, such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**.
- **Other significant events**:

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

3.1. ASSESSMENT OF SEVERITY

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the categories provided in Table 1 (as guidance for assessing adverse event severity). Further guidance on grading non-serious adverse events of special interest with regard to somnolence and sleep is provided in Appendix 9.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE V5.0] criteria); 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).

Table 1 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 above).

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, 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 treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study treatment, or reintroduction of study treatment.
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant 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.

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

4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Medical Monitor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology when available

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. 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 study. 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 treatment:

- Serious adverse events
- Non-serious adverse events of special interest (NSAESI) (see Section 8.3.6)
- Pregnancies (see Section 8.3.5)

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 IRB/EC.

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS, AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

Events that Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Events that Occur after Study Treatment Initiation

For reports of serious adverse events and non-serious adverse events of special interest (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

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

Reporting of Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other serious adverse event occurring after the end of the AE reporting period, if the event is believed to be related to prior study treatment the event should be reported directly to the Sponsor or its designee, either by

faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to Investigators.

5.2 REPORTING REQUIREMENTS FOR 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 participant, drug misuse could involve the drug being administered to someone other than the participant.

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). For RO7017773 and placebo, 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 RO7017773 and placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- 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 participant: Enter the drug name and "patient 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 the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

6. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and NSAESI 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 through use of the reference safety information in the document listed below:

Drug	Document
RO7017773	RO7017773 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.

Appendix 3
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.

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.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time 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 gastrointestinal 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.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

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

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:

- 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.
- 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., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

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:

- 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.
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

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. 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 Appendix 2) 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 a non-serious adverse event of special interest (see Section 8.3.6).

7. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor. This includes death attributed to worsening of comorbidities related to ASD.

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").

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”).

9. LACK OF EFFICACY OR WORSENING OF ASD

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 ASD symptoms on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., ”worsening of repetitive behaviors”).

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 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 participant has not suffered an adverse event.

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 for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

11. PATIENT-REPORTED OUTCOME DATA (COA DATA REPORTED DIRECTLY BY PARTICIPANTS)

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data. Roche/Genentech study team will determine whether any PRO data elements may be indicative of a medically significant adverse event (e.g., suicidal ideation, worsening of depression, worsening of hemoptysis) and could necessitate real time review by the site or Sponsor.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the central laboratory. If the local laboratory results are used, the results must be captured in source documentation and entered into the eCRF.

Local laboratory results are only required for the serum and urine pregnancy test and in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be captured in source documentation and entered as a comment into the eCRF}.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

All study-required laboratory assessments will be performed by a central laboratory, with the exception of the serum and urine pregnancy tests, as well as the dipstick test for urinalysis. Instruction manuals and supply kits will be provided for all central laboratory assessments. Laboratory test variables measured will include:

Laboratory Assessments	Parameters
Hematology	• Leukocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (absolute) (neutrophils, eosinophils, basophils, monocytes and lymphocytes)
Clinical Chemistry	• Sodium, potassium, chloride, bicarbonate, glucose (non-fasting) urea (BUN), creatinine, creatine phosphokinase (CPK), total protein, albumin, phosphate, calcium, magnesium, total bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), lactate dehydrogenase (LDH), HbA1c and GLDH (this last parameter will be optional; to be tested if the participant has elevated liver enzyme levels).
Coagulation	• Prothrombin time (INR), activated partial thromboplastin time (aPTT).

Laboratory Assessments	Parameters
Viral Serology	• HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody.
Lipids	• Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.
Thyroid Hormones	• Thyroxine (Free T4), thyroid stimulating-hormone (TSH)
Hormone	• Estradiol, follicle-stimulating hormone (FSH)
Pregnancy Test	• All women of childbearing potential (including those who have had a tubal occlusion/ligation) will have a blood pregnancy test at screening. At specified subsequent visits, urine sample will be used; tests results will be evaluated by the site's local laboratory. In case of a positive result on urine test, a confirmation with blood test has to be obtained. • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).
Urinalysis	• Dipstick: pH, glucose, protein, blood, will be performed at the study center (or directly at the participant's home in case of an unscheduled home visit, see Section 8.11.4). • If there is a clinically significant positive result, urine will be sent to the central laboratory for repeat urinalysis and reflex microscopy and culture, as needed. As per operator judgement, a second dipstick testing can be conducted beforehand for confirmation of the positive result. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture. • Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.
Other Tests	• Urine alcohol and drug screen (to include the following: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines). • SARS-CoV-2 could be tested through serology and/or respiratory swab at the discretion of the Investigator and Sponsor at screening and/or at any time during the study.

The results of each test must be entered into the eCRF if they are not uploaded to the database by the central laboratory.

Investigators must document their review of each laboratory safety report.

Based on continuous analysis of the data in this study, the Sponsor may decide at any time to stop the collection of any sample type not considered to be critical for safety if the data from the samples collected does not produce useful information.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing laboratory data include the use of Standard Reference Ranges and potential transformation of data for specific lab tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

- Definition of Laboratory Abnormalities

For all laboratory parameters included in the analysis described above, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for these laboratory parameters. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

- **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- **Women in the following categories are considered to be Woman of Non-Childbearing Potential (WONCBP)**

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

– Documented hysterectomy.

– Documented bilateral salpingectomy.

– Documented bilateral oophorectomy.

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

– A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

– Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use highly effective method of contraception consistently and correctly as described in Table 1 below.

Per ICH M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly as described in Table 1 below.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent [a] (Failure rate of < 1% per year when used consistently and correctly)

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Injectable

Highly Effective Methods That Are User-Independent (Failure rate of < 1% per year)
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion/ligation **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Acceptable Birth Control Methods Which May Not Be Considered As Highly Effective (Failure rate of > 1% per year when used consistently and correctly)
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide [b]
• Cap, diaphragm or sponge with spermicide [b]

a) Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b) A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods. i.e., when the risk of teratogenicity and genotoxicity is unlikely.

Male Participants

Male contraception is not required in this study because of the minimal seminal dose transmitted through sexual intercourse. Indeed, the exposure margins with a vaginal dose of RO7017773 after sexual intercourse (assuming 6 mL volume of semen) are approximately 49000 fold (rabbit/human) and 124000-fold (rat/human) based on embryo fetal development NOAEL in relevant species (Banholzer et al 2016).

3. PREGNANCY TESTING

For WOCBP enrolled in the study, blood and urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3).

In addition, pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

4. COLLECTION OF PREGNANCY INFORMATION

Female participants who become pregnant

The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment and will be withdrawn from the study.

5 ABORTIONS

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective or therapeutic abortion not associated with an underlying maternal or embryofetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Appendix 6
Examples of Prohibited Concomitant Medications

Please note that this is not an exhaustive list of prohibited medications.

Barbiturates

Allobarbital, amobarbital, aprobarbital, barbexaclone, barbital, butabarbital, cyclobarbital, ethallobarbital, heptabarbital, hexobarbital, hexobarbital, metharbital, methohexital, methohexital, methylphenobarbital, pentobarbital, phenobarbital, primidone, proxibarbal, reposal, secobarbital, talbutal, thiopental, thiopental, vinbarbital, vinylbital

Benzodiazepines and benzodiazepine-related drugs

Adinazolam, bromazepam, brotizolam, camazepam, chlordiazepoxide, cinolazepam, clobazam, clonazepam, clotiazepam, cloxazolam, diazepam, doxefazepam, estazolam, eszopiclone, ethyl loflazepate, etizolam, fludiazepam, flunitrazepam, flurazepam, halazepam, haloxazolam, ketazolam, loprazolam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordazepam, oxazolam, pinazepam, potassium clorazepate, prazepam, quazepam, temazepam, tetrazepam, tofisopam, triazolam, zaleplon, zolpidem, zopiclone

Other anxiolytics, hypnotics and sedatives (if used longer than 1 week in duration)

Acetyl glycinamide chloral hydrate, bromides, chloral hydrate, chloralodol, clomethiazole, dichloralphenazone, emylcamate, ethchlorvynol, mebutamate, meprobamate, methaqualone, paraldehyde

Anti-epileptic drugs

Phenelzine, tiagabine, vigabatrin, valproic acid, *topiramate, felbamate, zonisamide, pregabalin*
Note: see also CYP3A4 inducers for additional anti-epileptic drugs that are prohibited.

CYP3A inducers

Barbiturates, carbamazepine, efavirenz, systemic glucocorticoids, modafinil, nevirapine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort (hyperforin) mitotane, avasimibe, rifapentine, apalutamide, ivosidenib, enzalutamide, lumacaftor.

CYP3A inhibitors

Aprepitant, clarithromycin, fluconazole, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, verapamil, tipranavir, cobicistat (GS-9350), troleandomycin, telaprevir, danoprevir, elvitegravir lopinavir, voriconazole, mifepristone, mibefradil, posaconazole, ceritinib, conivaptan, nefazodone, ribociclib, idelalisib, and grapefruit juice.

Appendix 7
Alcohol Unit Calculation - Examples

From Australian Department of Health (Population Health Division)

http://www.alcohol.gov.au/internet/alcohol/publishing.nsf/Content/standard

Appendix 7
Alcohol Unit Calculation - Examples (cont.)

Appendix 8
List of Marketed Drugs Known to Prolong the QT Interval

Generic Name	Brand Names (Partial List)	Drug Class
Aclarubicin (non-U.S. market only)	Aclacin, Aclacinomycin, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor
Arsenic trioxide	Trisenox	Anti-cancer
Azithromycin	Zithromax, Zmax	Antibiotic
Chloroquine	Aralen	Antimalarial
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic
Citalopram	Celexa, Cipramil	Antidepressant, SSRI
Clarithromycin	Biaxin, Prevpac	Antibiotic
Cocaine	Cocaine	Local anesthetic
Disopyramide	Norpace	Antiarrhythmic
Dofetilide	Tikosyn	Antiarrhythmic
Domperidone (non-U.S. market only)	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic
Donepezil	Aricept	Cholinesterase inhibitor
Dronedarone	Multaq	Antiarrhythmic
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic

Generic Name	Brand Names (Partial List)	Drug Class
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	Antidepressant, SSRI
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic
Fluconazole	Diflucan, Trican	Antifungal
Halofantrine (non-U.S. market only)	Halfan	Antimalarial
Haloperidol	Haldol (U.S. & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic
Hydroquinidine (Dihydroquinidine) (non-U.S. market only)	Serecor	Antiarrhythmic
Ibogaine (non-U.S. market only)	None	Psychedelic
Ibutilide	Corvert	Antiarrhythmic
Levofloxacin	Levaquin, Tavanic	Antibiotic
Levomepromazine (Methotrimeprazine) (non-U.S. market only)	Nosinan, Nozinan, Levoprome	Antipsychotic
Levosulpiride (non-U.S. market only)	Lesuride, Levazeo, Enliva (with rabeprazole)	Antipsychotic
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic

Generic Name	Brand Names (Partial List)	Drug Class
Oxaliplatin	Eloxatin	Anti-cancer
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary
Pentamidine	Pentam	Antifungal
Pimozide	Orap	Antipsychotic
Procainamide	Pronestyl, Procan	Antiarrhythmic
Propofol	Diprivan, Propoven	Anesthetic, general
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic
Roxithromycin (non-U.S. market only)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycin, Roxomycin, Rulide, Tirabicin, Coroxin	Antibiotic
Sevoflurane	Ultane, Sojourn	Anesthetic, general
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic
Sulpiride (non-U.S. market only)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical
Sultopride (non-U.S. market only)	Barnetil, Barnotil, Topral	Antipsychotic, atypical
Terlipressin (non-U.S. market only)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others	Vasoconstrictor
Terodiline (non-U.S. market only)	Micturin, Mictrol (not bethanechol)	Muscle relaxant
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic
Vandetanib	Caprelsa	Anti-cancer

Source https://crediblemeds.org/new-drug-list/ - Last revision date: September 15, 2019

Appendix 9
Grading for Adverse Events of Special Interest with Regard to Somnolence and Sleep

Term	Grade 1 -Mild	Grade 2 – Moderate	Grade 3 -Severe	Definition	Source
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	Excessive sleepiness during the daytime.	CTCAE V5.0
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Excessive sleepiness and drowsiness.	CTCAE V5.0
Depressed Level of Consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	A disorder characterized by a decrease in ability to perceive and respond	CTCAE V5.0
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	No CTCAE V5.0 grade 3	A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.	CTCAE V5.0
Sudden Onset Sleep	no or mild disruption or work/activities/ social life	moderate disruption or work/activities/ social life	important disruption or work/activities/ social life	A sensation of sudden, irresistible, daytime sleepiness without awareness of falling asleep	Roche internal

ADL = activities of daily living

Appendix 10
Preferred Term Examples for Gastrointestinal Adverse Events of Special Interest

Source: MedDRA Version 22.1 Standardised MedDRA Queries (SMQ)
Gastrointestinal non-specific symptoms and therapeutic procedures (SMQ-narrow)

Abdominal discomfort
Abdominal distension
Abdominal pain
Abdominal pain lower
Abdominal pain upper
Abdominal symptom
Abdominal tenderness
Abnormal faeces
Aerophagia
Anorectal discomfort
Bowel movement irregularity
Change of bowel habit
Constipation
Defaecation urgency
Diarrhoea
Epigastric discomfort
Eructation
Faecal volume decreased
Faecal volume increased
Faeces hard
Faeces soft
Flatulence
Frequent bowel movements
Gastrointestinal pain
Gastrointestinal sounds abnormal
Gastrointestinal toxicity
Infrequent bowel movements
Nausea
Non-cardiac chest pain
Oesophageal discomfort
Oesophageal pain
Premenstrual cramps
Vomiting

Appendix 11
Supplementary Information for Digital Biomarkers

PARTICIPATION: BENEFITS, TRAINING, AND COMPLIANCE

WHAT IS THE BENEFIT OF COLLECTING THESE DATA?

The traditional approaches to measuring the signs and symptoms of a condition, through the report of a participant, observer, or clinician, have a variety of drawbacks. Reports can be unreliable due to the dependence on subjective ratings. They require the participant to visit a clinical site and this may require travelling a long distance and the time taken to administer the assessments can be great, creating a high burden for the participant. The frequency of measurement is low; therefore, changes in symptom severity in-between site visits is not captured. If symptom severity is much higher on the day of the visit, this will give a misleading impression of their status. Digital Health Technology has the potential to address these drawbacks by measuring the signs of a condition objectively, remotely and frequently using sensor technology that can be used independently by participants in their daily life. This study will explore the feasibility of using this technology in this cohort.

IS A PARTICIPANT OBLIGED TO COMPLETE A TASK IF THEY FIND THE DIGITAL BIOMARKER SCHEDULE OF ASSESSMENTS TOO DEMANDING?

We encourage participants to complete the tasks at home as per the digital biomarker schedule of assessments, but if a participant does not complete a task on one or more days this will not count as a protocol deviation.

IS A PARTICIPANT OBLIGED TO COMPLETE A TASK IF THEY ARE UNABLE TO UNDERSTAND THE INSTRUCTIONS?

The tasks are designed to be simple to understand and full instructions are provided in the application. Participants are then provided with full training by site staff. Some participants may, however, remain unable to understand the task instructions. Understanding instructions may be particularly problematic for those participants with intellectual disability. In such cases site staff can de-activate the task for that participant.

ARE ALL PARTICIPANTS OBLIGED TO WEAR THE SMARTWATCH?

When the participant consents to the study, they agree to wear the smartwatch on a daily basis, but if a participant does not wear the smartwatch on one or more days this will not count as a protocol deviation.

ARE ALL PARTICIPANTS OBLIGED TO INSTALL THE BEACONS?

The use of the beacons is optional. If the participant agrees to install the beacons in their home but *subsequently* does not, this will not count as a protocol deviation.

ARE ALL PARTICIPANTS OBLIGED TO INSTALL THE SLEEP MAT?

When the participant consents to the study they agree to install the sleep mat under their mattress, but if a participant does not install the sleep mat this will not count as a protocol deviation.

HOW ARE PARTICIPANTS TRAINED ON HOW TO USE THE TECHNOLOGY?

Site staff will provide participants with full training on the tasks. Site staff receive extensive training from the Sponsor.

HOW LONG DO THE TASKS TAKE?

In total the three active tasks take on average 5 minutes per week to complete. In addition to this, we ask the participants to record a conversation of up to 5 minutes' duration with the support person at least once per week.

HOW IS POOR COMPLIANCE HANDLED?

Statistics on compliance are provided in the smartphone application and on a secure website. The Sponsor, monitors and site staff will have access to the secure website. This allows the participant, monitors and site staff to monitor compliance. Site staff should encourage good compliance when they have contact with the participant.

TECHNOLOGY: LOGISTICS AND SUPPLY

WHAT ARE THE MAKES AND MODELS OF THE TECHNOLOGY BEING USED?

The smartphone is a Samsung Galaxy A40. The smartwatch is the Samsung Galaxy Watch Active. Each People Beacon is a Kontakt S18-3. Each Room Beacon is a Kontakt S16-2. The sleep mat is an Emfit QS sleep sensor.

HOW IS THE TECHNOLOGY STORED AND SUPPLIED TO SITES?

The technology is purchased by the Sponsor. The Sponsor then installs custom software developed by the Sponsor on the technology and stores it until it is shipped either directly to a site, or via a depot managed by the Sponsor. If a depot is used the depot will temporarily store the technology before shipping to a site. The site should then store the technology until handing it over to a participant. When the technology is returned to a site, the site should store it until the Sponsor arranges a return shipment, either directly to the Sponsor or via the depot.

WHAT PROCEDURES ARE IN PLACE IF A PARTICIPANT DAMAGES OR LOSES THE TECHNOLOGY?

If a participant damages or loses any of the technology they should contact the site to arrange a replacement. The site is responsible for recording the damage or loss of

equipment in the device sheet that is included with the technology and the eCRF. The device sheet should then be scanned and emailed to Roche at the contact address provided with the training material.

DATA SECURITY AND PRIVACY

DO YOU CAPTURE ANY PERSONALLY-IDENTIFIABLE INFORMATION?

The participant's name and other identifiable text are not captured. The site is asked to enter the participant's screening ID into the smartphone application and all other data captured with the technology is then related to the participant through the screening ID. Please see questions below for issues related to location and audio data.

HOW IS DATA SECURITY MAINTAINED?

Once the data have been collected, the data are encrypted using industry gold standard 256-bit asymmetric encryption. This encryption method makes it impossible for anyone, including the study participant, to decrypt and read the data. The data can only be decrypted and processed by named researchers of the Sponsor. Whenever the study participant connects to Wi-Fi, the data are transmitted via a secure transfer protocol (HTTPS) to a secure cloud (Microsoft Azure).

Data from a participant are uploaded to the Microsoft Azure server located in the Netherlands. The Microsoft Azure cloud servers are managed by the Sponsor. Upon successful data transfer, the data copy on the smartphone is deleted. Data on the secure cloud remain asymmetrically encrypted at all times. For data processing and analysis purposes, data are mirrored from the secure cloud to one of the Sponsor's physical servers that are located behind the Sponsor's firewall. Here data are decrypted by named researchers. The data are then processed for the computation of features from the sensor data.

HOW WILL THE AUDIO RECORDINGS BE PROCESSED TO PROTECT THE CONFIDENTIALITY OF THE PERSON(S) BEING RECORDED?

Audio is recorded on the smartphone (only) during the Describe the Picture task and Conversation task. At the end of each task participants have the option to delete the recording. If they agree to transfer the recording, it will be uploaded to the Sponsor via the secure server described above. The audio recordings may then be listened to by a small, limited number of researchers employed by the Sponsor. Features will be derived from the audio recordings for analysis. These features will not include personally-identifiable information. There will be a delay between the audio recordings being recorded, transferred to the Sponsor, and analyzed by the Sponsor, potentially lasting up to many months; therefore, the recordings will not be used for detecting adverse events.

Background noise is also recorded continuously by the smartphone application. Statistical features of these data are extracted by the smartphone application. The raw audio recordings are not stored on the smartphone – they are held in temporary memory and discarded after extraction of the statistical features. The statistical features are then transferred to the Sponsor via the server described above. These statistical features allow one to infer the volume and duration of speech in the environment, but not the actual words spoken.

HOW IS LOCATION DATA PROCESSED TO PROTECT PARTICIPANT PRIVACY?

GPS location data are obfuscated at data capture. From the obfuscated data it is not possible to determine the participant's actual location, only the direction and distance that they travel. Specifically, the data points are translated into latitudinal and longitudinal direction and also rotated using a certain factor within their natural ranges of -90° : +90° for latitude, -180° : +180° for longitude and 0° : 360° for rotation.

REMOTE ADMINISTRATION OF IN-CLINIC ASSESSMENTS FOR DIGITAL BIOMARKERS

In the event that the study participant and support person are not able to access their clinical site to attend in-clinic visits as scheduled per Table 3, in-clinic assessment for the digital biomarkers might be administrated remotely in a telemedicine visit (e.g., phone call, virtual meeting) set up to best fit patient's and support person's needs as well as site capabilities. Remote in-clinic assessments are in any case to be performed under the supervision (in–remote) of study site personnel, who should provide support as needed to study participant and support person. Within the study phone app, a remote in-clinic assessment feature has been built and it is unattained password protected. This function is not hosted in the clinician area, but is specifically designed to be accessed only by study participants. Detailed guidance will be provided to the study sites for remote administration of the in-clinic assessment for digital biomarkers.

Remote assessments should be scheduled within the corresponding visit window and can only be done if the participants have access to a location where privacy can be assured and distractions kept to a minimum.

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