F. HOFFMANN-LA ROCHE LTD
CLINICAL STUDY PROTOCOL
PROTOCOL NUMBER NP25620
RO4917523
EUDRACT NUMBER 2011-001436-33
IND NUMBER 103001

Sponsor: F. HOFFMANN-LA ROCHE LTD
Grenzacherstrasse 124,
4070 Basel, Switzerland

PROTOCOL APPROVAL

Protocol Number / Version: NP25620 / C

Date: See date in electronic signature manifestation below.

Name | Reason for Signing | Date and Time
--- | --- | ---
Quiroz,Jorge | Translational Medicine Leader | 04-Apr-2012 18:04:29

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SYNOPSIS OF PROTOCOL NUMBER NP25620

TITLE A randomized, double-blind, parallel-group study of the safety and efficacy of RO4917523 versus placebo, as adjunctive therapy in patients with major depressive disorder with inadequate response to ongoing antidepressant treatment.

SPONSOR F. Hoffmann-La Roche Ltd

INDICATION Major Depressive Disorder (MDD)

OBJECTIVES

Primary
To evaluate the efficacy of two fixed doses of RO4917523 compared to placebo in a confirmatory manner over 6 weeks as adjunctive therapy in patients with MDD with inadequate response to ongoing antidepressant treatment, based on mean change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

Secondary
The secondary objectives are to evaluate change after 6 weeks of treatment with RO4917523 versus placebo as adjunctive therapy on the following:

- Clinical Global Impression Scores: Severity (CGI-S) from baseline to end of treatment, and Improvement (CGI-I) at end of treatment
- Safety and tolerability of RO4917523
- Proportion of patients exhibiting remission (a MADRS score of less than or equal to 10)
- Proportion of patients exhibiting response (reduction in MADRS score equal to or greater than 50% of the baseline score)
- Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16)
- Patient Global Impression of Improvement (PGI-I) score at end of treatment

Exploratory

Key Exploratory Objective
To evaluate the effect size (ES) of two fixed doses of RO4917523 compared to placebo over 6 weeks as adjunctive therapy in patients with MDD with inadequate response to ongoing antidepressant treatment, based on mean change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

Other Exploratory Objectives
To investigate the differential effect of RO4917523 vs. placebo in:

- Proportion of patients who meet MADRS responder criteria plus CGI-I score of 1) "very much improved" or 2) "much improved"
- Proportion of patients who meet MADRS remission criteria plus CGI-I score of 1) "very much improved" or 2) "much improved"
- Speed of onset of antidepressant effect based on change over time in any of the depression symptom scales
- CANTAB Cognitive Test Battery subset
- Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)
- Sheehan Disability Scale (SDS)
Pharmacokinetics

- Pharmacokinetics of RO4917523 in the target population with the objective of performing a population pharmacokinetic analysis with non-linear mixed effect model

Biomarkers

- Identify biomarkers that are predictive of response to RO4917523 treatment
- Increase our knowledge and understanding of the pathogenesis, course and outcome of depression and related diseases
- Develop biomarker or diagnostic assays, and establish the performance characteristics of these assays

TRIAL DESIGN

This is an outpatient trial consisting of three consecutive periods: screening (up to 14 days), 6-week double-blind treatment, and a 21 day follow-up period.

NUMBER OF SUBJECTS

Approximately 300 patients, randomized in equal proportions to the three treatment arms.

TARGET POPULATION

The study will include male and female outpatients from 18 to 70 years of age with a primary diagnosis of major depressive disorder (MDD) without psychotic features as defined by DSM-IV-TR criteria, and having inadequate response to ongoing antidepressant therapy. Patients must have had at least one but no more than three treatment failures (of adequate dose and duration according to the Massachusetts General Hospital Antidepressant Treatment History Questionnaire [MGH ATRQ]). Failure to ongoing antidepressant treatment in the current episode is counted as one treatment failure.

LENGTH OF STUDY

- 14 day screening period
- 6 week double-blind treatment
- 21 day follow-up

END OF STUDY

The date of the last visit (including the follow-up period) of the last patient in the study

INVESTIGATIONAL MEDICAL PRODUCT(S)

Doses of RO4917523 0.5 mg or 1.5 mg supplied as pellets in capsules, in combinations of Ro 491-7523/F18 0.5 mg, Ro 491-7523/F19 1.0 mg, taken orally once a day

COMPARATOR “DRUG”

Matching capsules of placebo Ro 491-7523/F21, taken orally once a day

ASSESSMENTS OF:

- EFFICACY
  - MADRS total score
  - Remission (a MADRS score less than or equal to 10)
  - Response (reduction in MADRS score equal to or greater than 50% from baseline)
  - CGI-S
  - CGI-I
  - PGI-I
  - QIDS-SR16
  - Q-LES-Q-SF
  - SDS
  - CANTAB
SAFETY

- Adverse events (AEs) and concomitant medications will be monitored throughout the entire study (screening through follow-up). Intensity of AEs will be graded on a 3 point scale (mild, moderate, or severe)
- A subscale (4 items) of the BPRS will be completed only to follow up on treatment emergent psychotic-related and mania-related (mania or hypomania) adverse events. The symptom constructs included are conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content
- The YMRS (item 1 only for mood elevation) will be completed only to follow up on treatment emergent psychotic-related and mania-related (mania or hypomania) adverse events
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Physical examination
- Vital signs (pulse, blood pressure)
- 12-lead ECG
- Laboratory parameters
  - Chemistry panel
  - Hematology panel with differential
  - Free T4 and TSH
  - Viral Serology
  - Urinalysis (dipstick)
  - Urine drug screen
  - Pregnancy test in females
- Data Safety Monitoring Board (DSMB)
  - An independent Data Safety Monitoring Board (DSMB) will review potential safety signals of concern. The DSMB will be composed of non-sponsor members who are not involved in the conduct of this study. The DSMB will review available safety data from this trial at regularly scheduled intervals as specified in the DSMB Charter
- Statistical Interim Analyses
  - No statistical interim analyses are planned

PHARMACOKINETICS

PK sampling will be obtained from all patients according to the Schedule of Assessments.

EXPLORATORY - BIOMARKERS (non-inherited)

Specimens for the Roche Clinical Repository (RCR) will be collected for dynamic (non-inherited) biomarker discovery and validation. The RCR sampling is optional. Blood specimens will be collected as per Schedule of Assessments, with details as follows:

Plasma and Serum assays: Blood samples for plasma and serum isolation will be obtained at baseline and the end of treatment. A total of 4 samples (2x6 mL for serum and 2x6 mL for plasma; 24 mL total) for each patient will be collected during the study. These samples will be used for biomarker assays for candidate depression biomarkers.

Blood for RNA expression profiling: Blood samples for RNA isolation will be obtained at baseline and the end of treatment (5 mL each; 10 mL total).

Blood sample for epigenetic analysis: Blood samples for DNA isolation will be collected at baseline and the end of treatment (6 mL each; 12 mL total).

These specimens will be stored for up to 15 years after the end of the study.
Additional specimens for the Roche Clinical Repository (RCR) will be collected from consenting patients for genetic biomarker (inherited) discovery and validation. The RCR sampling (inherited) is optional. A single blood specimen will be collected from consenting patients, with details as follows:

- **Blood sample for genetic analysis**: A blood sample (approx. 6 mL) for DNA isolation will be collected at a single study visit as per Schedule of Assessments. If however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected at any time (after randomization) during the conduct of the clinical study. The sample may be processed using techniques such as sequencing or microarray profiling. These specimen(s) will be stored for up to 15 years after the end of the study.

Blood samples for serum and plasma protein biomarker discovery and validation will be collected from all patients where permissible with local regulations at baseline and the end of treatment. A total of 4 samples (2x6 mL for serum and 2x6 mL for plasma; 24 mL total) for each patient will be collected during the study. These specimens will be destroyed no later than 5 years after the end of the study.

A 3 mL whole blood sample will be taken for DNA extraction from all patients where permissible with local regulations at baseline. The DNA will be tested for one or more of the following specific genes: the cytochrome P450 variant 1A2 gene (CYP1A2), the metabotropic glutamate receptor 5 (GRM5), the serotonin 2A receptor (HTR2A), the serotonin transporter (SLC6A4), and brain derived neurotropic factor (BDNF). This specimen will be destroyed immediately after the analysis has been completed.

**PROCEDURES (summary): Screening Period (up to 14 days)**

During the screening period, informed consent will be obtained, and the investigator will determine whether the candidate meets all inclusion criteria and does not meet any exclusion criteria.

**6-Week Double-blind Treatment Period**

In order to be randomized into the double-blind treatment period, patients must have at baseline:

- No significant risk of suicidal behavior (e.g., consider the Suicidal Ideation section of the C-SSRS “Since Last Visit” for this evaluation)

- No significant change in medical or psychiatric condition, or change in medications since screening (unless agreed with the Sponsor/Medical Monitor)

- Negative result on the Baseline pregnancy test (if applicable)

- No change in ongoing antidepressant therapy, and ability to continue for the duration of the double-blind treatment period without modification to the dosing schedule

- An ESF/EAF approved by the Sponsor/Medical Monitor
The double-blind treatment period begins with the investigational site call into IVRS confirming the patient’s eligibility. The patient will be randomized and receive their first dose of study medication on Day 1.

Dose 1 of the blinded study medication is to be administered in the clinic immediately after a meal and before 12 pm (noon), or soon thereafter upon consultation with the Sponsor/Medical Monitor, once all baseline procedures and assessments are completed. Patients will remain at the clinic for 6 hours after the first dose for safety monitoring and for the PK samples (according to clinical observation and patient availability). Subsequently, dosing will be once daily in the morning immediately after breakfast.

As with any experimental drug at this stage of development, it is advisable for patients not to drive or operate dangerous machinery until known side effects (e.g., dizziness and somnolence) can be adequately assessed on an individual basis during the trial.

Patients will arrive at each study visit without having taken their daily dose of study medication, and site staff will record the time of their last dose. Following collection of the pre-dose PK blood sample (if applicable) and a meal, patients will take their next dose of study medication before 12 pm (noon) or soon thereafter upon consultation with the Sponsor/Medical Monitor. The last dose of study medication will be administered on Day 42 (End-of-Treatment visit).

Early Discontinuers will be instructed to return as soon as possible for the End-of-Treatment visit, and 21 days later for the Follow-up visit.

**Follow-up Period (21 days)**

A Follow-up Visit will take place 21 days after the End-of-Treatment visit. During the follow-up period, adjustments to antidepressant treatments may be initiated if deemed necessary by the investigator.

**STATISTICAL ANALYSES:**

Main efficacy analysis will be performed in a confirmatory manner based on ITT population, using a mixed effects covariance pattern model (MMRM) to utilize all the data collected over time. A closed testing procedure will be used to take multiple comparisons into account. As supporting analysis, the analysis may be repeated on the per-protocol population. Another supportive analysis will use an ANCOVA with LOCF imputation for missing data. The primary efficacy variable is change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

All safety variables (e.g., adverse events, lab tests, ECG, vital signs, BPRS, YMRS, ASEX) will be summarized for each assessment time (including follow-up) using descriptive statistics. The items of the C-SSRS will be presented by individual listings and the outcomes from this scale will be classified using the C-CASA methodology.
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<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
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<tr>
<td>ALT [SGPT]</td>
<td>alanine aminotransferase</td>
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<tr>
<td>AMPA</td>
<td>α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate</td>
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<td>ANCOVA</td>
<td>analysis of covariance</td>
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<td>AST [SGOT]</td>
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<td>AUC</td>
<td>area under the plasma concentration-time curve</td>
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<td>BDNF</td>
<td>brain-derived neurotrophic factor</td>
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<tr>
<td>b.i.d.</td>
<td>Latin bis in die (twice a day)</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>BP</td>
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<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
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<tr>
<td>CFF</td>
<td>critical flicker fusion test</td>
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<td>CG</td>
<td>clinical genotyping</td>
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<td>C-CASA</td>
<td>Columbia Classification Algorithm of Suicidality Assessment</td>
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<td>CANTAB®</td>
<td>Cambridge Neuropsychological Test Automated Battery</td>
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<td>CDS</td>
<td>core data sheet</td>
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<td>CGI-I</td>
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<td>CGI-S</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CL</td>
<td>plasma clearance</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>C_max</td>
<td>maximum plasma concentration</td>
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</tr>
<tr>
<td>CPK</td>
<td>creatine phosphokinase</td>
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</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
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### GLOSSARY OF ABBREVIATIONS

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<tr>
<td>CRO</td>
<td>contract research organization</td>
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<tr>
<td>CRT</td>
<td>choice reaction time</td>
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<td>C-SSRS</td>
<td>Columbia-Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>CSR</td>
<td>clinical study report</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P</td>
</tr>
<tr>
<td>DCS</td>
<td>data collection specification</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision</td>
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<tr>
<td>DSST</td>
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<td>Diagnostic Validation-Major Depressive Disorder</td>
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<td>electrocardiogram</td>
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<td>Ethylenediaminetetraacetic acid</td>
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<td>European Economic Area</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FSH</td>
<td>follicle stimulating hormone</td>
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<td>FTP</td>
<td>file transfer protocol</td>
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<td>GABA</td>
<td>gamma-aminobutyric acid</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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GLOSSARY OF ABBREVIATIONS

GGT  gamma-glutamyltransferase
GI  gastro intestinal
GLP  Good Laboratory Practice
HDL  high density lipoprotein
HIV  human immunodeficiency virus
HPLC  high performance liquid chromatography
HR  heart rate
IB  Investigator Brochure
IC50  inhibitory concentration, half maximal
ICD-10  The International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICF  Informed Consent Form
ICH  International Conference on Harmonization
ID  identification
IEC  Independent Ethics Committee
iGlu  ionotrophic glutamate
IMP  investigational medicinal product
IND  investigational new drug application
INR  International Normalized Ratio
IP  internet protocol
IR  immediate release
IRB  Institutional Review Board
ITT  intent to treat
IUD  intrauterine device
iv  intravenous
IVRS  interactive voice response system
IWRS  interactive web response system
GLOSSARY OF ABBREVIATIONS

k\text{eq} \quad \text{equilibration rate constant}

k_d \quad \text{dissociation rate constant}

LC/MS/MS \quad \text{liquid chromatography/tandem mass spectrometry}

LDL \quad \text{low density lipoprotein}

LMT \quad \text{learning memory task}

LOCF \quad \text{Last observation carried forward}

MAD \quad \text{multiple ascending dose}

MADRS \quad \text{Montgomery Asberg Depression Rating Scale}

MBS \quad \text{Mandatory Biomarker Samples}

MDD \quad \text{Major depressive disorder}

MGH ATRQ \quad \text{Massachusetts General Hospital Antidepressant Treatment Response Questionnaire}

mGlu \quad \text{metabotropic glutamate}

MINI \quad \text{Mini International Neuropsychiatric Inventory}

MMRM \quad \text{mixed effect repeated measure analysis}

MPEP \quad 2\text{-methyl-6-(phenylethynyl)-pyridine}

MR \quad \text{modified release}

MTD \quad \text{maximum tolerated dose}

MTEP \quad [(2\text{-methyl-1,3-thiazol-4-yl})\text{ethynyl}]\text{pyridine}

NMDA \quad \text{N-methyl-D-aspartic acid}

NOEL \quad \text{No observed effect level}

NOAEL \quad \text{No observed adverse effect level}

OCD \quad \text{Obsessive-Compulsive Disorder}

OB \quad \text{olfactory bulbectomized}

PCP \quad \text{Phencyclidine}

PD \quad \text{Pharmacodynamic}

PE \quad \text{Pharmacoeconomic}
GLOSSARY OF ABBREVIATIONS

PGI-I Patient Global Impression of Improvement
PI principal investigator
PK pharmacokinetic
PP per protocol
PR pulse rate
PTSD Postraumatic Stress Disorder
QD Latin quaque die (every day)
QIDS-SR16 Quick Inventory of Depressive Symptomatology-Self Report, 16 item version
Q-LES-Q-SF Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form
RCR Roche Clinical Repository
REM rapid eye movement
RNA ribonucleic acid
RT PCR reverse transcriptase polymerase chain reaction
RVIP rapid visual information processing
SAD single ascending dose
SAE serious adverse event
SDS Sheehan Disability Scale
SEM saccadic eye movement
sFTP secure file transfer protocol
SMT study management team
SNRI serotonin and norepinephrine reuptake inhibitor
SPC Summary of Product Characteristics
SSRI selective serotonin reuptake inhibitor
SUSAR Suspected Unexpected Serious Adverse Reaction
T3 triiodothyronine
T4 thyroxine
## GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>t.b.d.</td>
<td>to be determined</td>
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<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>terminal elimination half life</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>time of maximal concentration</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
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<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
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<tr>
<td>V&lt;sub&gt;SS&lt;/sub&gt;</td>
<td>volume of distribution at steady state</td>
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<tr>
<td>VAS</td>
<td>Bond-Lader visual analog scale</td>
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<td>YMRS</td>
<td>Young Mania Rating Scale</td>
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PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 Background

Glutamate is the main excitatory neurotransmitter that mediates its effects via ionotropic glutamate (iGlu) receptors (NMDA, AMPA and kainate receptors) and metabotropic glutamate (mGlu) receptors (G-protein coupled receptors). There are currently eight known mGlu receptors that are classified into three clusters based on sequence homology, preferred signal transduction pathway, and pharmacology. Group I includes mGlu1 and mGlu5 receptors, which are coupled via Gq to phospholipase C. Group II includes mGlu2 and mGlu3 receptors, and Group III includes mGlu 4, 6, 7 and 8 receptors, all of which are coupled to Gi and inhibit cAMP formation.

The mGlu5 receptor has emerged as an attractive target for the treatment of anxiety and depressive disorders based on its expression pattern in the brain and the efficacy of mGluR5 antagonists in various animal models of these diseases. mGlu5 receptors are highly expressed in limbic areas of the brain including the limbic cortex, the hippocampus, the amygdala and the basal ganglia. These areas are known to be involved in emotional and motivational processes and play a critical role in affective disorders including anxiety and depression. A general review of the relevance of the glutamatergic system in the treatment of mood disorders is provided by Sanacora et al [1].

There is evidence from nonclinical and clinical studies to suggest that glutamatergic dysfunctions may be involved in the pathophysiology of depression, and that interventions aimed to modify the glutamatergic neurotransmission may possess antidepressant effects. In fact, the prototypical mGluR5 antagonists MPEP and MTEP have been shown to induce positive results in the forced swim test and tail suspension tests animal models of depression. Additional supportive evidence has been originated from olfactory bulbectomized rats (a different animal model) on which known chronic (but not acute) anti-depressant treatment selectively reduce passive avoidance deficits and hyperactivity, also reversed by MPEP and MTEP administration. Recent clinical data indicate that ketamine, an NMDA channel blocking agent, has a fast acting (within hours) antidepressant-like effect in treatment-resistant patients [2]. Given the co-localization of NMDA receptors and mGlu5 receptors in the limbic regions, and that the downstream effects of mGlu5 receptor blockade are related to down-regulation of NMDA function, there is a strong rationale for antidepressant-like activity for mGlu5 receptor antagonists.

1.1.1 Disease

Major Depressive Disorder (MDD) remains an area of considerable medical need despite the many agents approved for treatment of this illness. Response rates for initial treatment are estimated to be about 50%, while remission, considered to be the goal of treatment, ranges from 15 to 40% [3]. The recently published results of the STAR*D trial have provided sobering conclusions regarding the conceptualization of remission and its implications for defining recovery, relapse, and recurrence [4]. The study showed that only one-third of patients achieved remission with initial treatment, and remission rates declined even further with each successive treatment attempt (36.8% after first, 30.6%
after second, 13.7% after third and 13% after fourth treatment). Moreover, various switching strategies employed as second-line treatment did not yield very different results [5].

Failure to obtain remission, therefore, is a common clinical problem. Patients who are treatment resistant use a disproportionately larger share of health care resources, have significantly more claims for comorbid conditions, and cost employers more in lost productivity compared with patients with major depression who respond to treatment. Given the disabling impact of persistent depression and its medical consequences, one can argue that new treatments addressing inadequate response to antidepressant therapy in MDD would fulfill an important medical need.

1.1.2 Study “Drug”

RO4917523 will be provided in capsules for this study. Further information is provided in Section 6, Investigational Medicinal Product.

1.2 Non-Clinical Experience

1.2.1 Non-Clinical Pharmacology

In vitro, RO4917523 has been shown to be a potent mGlu5 receptor antagonist (Kd of 0.8 nM for human mGlu5 receptors). When RO4917523 was tested for activity on other relevant targets (over 100), it exhibited over 1000-fold lower activity at all targets including receptors, enzymes and ion channels. In animal models of anxiety, RO4917523 elicits dose-dependent anxiolytic effects in the Stress-Induced Hyperthermia (SIH) model in mice, in the Vogel Conflict Test in rats, the Fear Potentiated Startle response in rats, and in the Conditioned Emotional Response (CER) tests in rats. Furthermore, RO4917523 was also active in animal models used to detect antidepressant potential such as the forced swim test and the stress-induced anhedonia test. In sleep studies, RO4917523 induced an increase in non-REM:REM ratio supportive of an anti-depressant-like profile. RO4917523 did not potentiate the effects of ethanol in mice and had no cognitive impairing activity in the delayed match to position test in rats. However, RO4917523 impaired performance in the Morris water maze in two different protocols at doses above 0.1 mg/kg p.o. at 4 h post-administration.

1.2.2 Non-Clinical Pharmacokinetics and Metabolism

The estimated (single dose) volume of distribution at steady state (Vss) of RO4917523 was generally high in animals, 4 and 5 L/kg in rats and monkeys, respectively. The total plasma clearance (CL) was low to moderate, approximately 6 and 9 mL/min/kg in rat and monkeys, respectively. The terminal elimination half-life (T1/2) values were between 7.5 to 10 h in rat and monkey.

RO4917523 was well absorbed after oral administration and had a high oral bioavailability in rodents and cynomolgus monkey. In monkeys, the bioavailability was higher in fasted animals.

Plasma protein binding is expected to be high in man. The in vitro bound fraction was approximately 95 to 98 %, respectively, in animal and human plasma. RO4917523 showed a moderate partitioning to blood cells with an in vitro blood/plasma concentration
ratio of 1.3 in rat blood and penetrated well into brain tissue. The brain to plasma concentration ratio in the rat ranged from 1.7 to 2.9.

The results of in vitro drug metabolism studies suggest that RO4917523 is predominantly metabolized to hydroxy-metabolites by cytochrome P450 enzymes (CYP 1A1, 1A2, 2C9, 3A4, 3A5). CYP 3A isoforms were responsible for > 90% human liver microsomal metabolism.

Mass balance studies in rats with [14C]-RO4917523 indicate complete excretion within 120 h of administration. 20% and 80% of total drug radioactivity was recovered in urine and feces, respectively. Quantitative whole body autoradiography revealed elevated concentrations of radioactivity in the inner cortex of the kidney, the liver, thyroid gland and nasal mucosa at 6 h. In cynomolgus monkeys, approximately 82% of the total radioactivity was recovered after 168 h postdose, excreted mainly in the feces.

1.2.3 Non-Clinical Safety and Toxicology

In repeat-dose toxicity studies, the main targets for RO4917523-related systemic toxicity were the CNS, which is the pharmacological target, and as an adaptive response to drug load, the liver. Other organs (pituitary, thyroid, adrenals) were most probably secondarily affected. Chronic toxicity studies in rats and monkeys are currently ongoing.

Based on the available non-clinical safety information, the overall NOAEL for general toxicology effects is considered to be 4 mg/kg/day in adult and 10 mg/kg/day in juvenile rats, and 10 mg/kg/day in monkeys. In rat fertility studies the NOAEL for male mating performance was 1 mg/kg/day and for female fertility 0.3 mg/kg/day.

CNS-related effects were transiently observed in rats in general toxicology studies on the first or first few study days. They included drowsiness and hypoactivity. In CNS safety pharmacology studies in rats, the effects also included gait abnormalities, changes in body posture and body tone, and a transient decrease in body temperature, and after the occurrence of these early effects, slightly increased exploratory behavior from 2 to 6 hours post dose. There was no obvious dose-effect relationship.
The NOEL for the CNS-effects is ≤ 0.1 mg/kg in rats (maximal effect reached at 0.5-1 mg/kg without any further increase at higher doses. In rats, because of their low degree, transient nature with fast recovery, and occurrence on the first day or first few days of dosing only, and in monkeys, because of their low degree and inconsistent presence at doses ≤30 mg/kg, and because of ease of monitoring in humans, these effects are not considered ‘adverse’ from a safety perspective, but rather signs of exaggerated pharmacological activity.

The mechanism of these CNS effects is not known, but it is assumed that at the lower doses they are secondary effects of the mGlu5-antagonism of RO491723. Other mGlu5-antagonists have been reported to decrease locomotor activity, impair Rotarod performance and decrease body temperature. At the higher dose levels also off-target mechanisms may be involved.

Minor hepatic findings (minimal to slight liver cell hypertrophy), most likely related to the high drug load, were consistently only seen in rats (NOAEL 4 mg/kg/day). In clinical chemistry the most prominent change in rats was a 12-fold increase in GGT at 100 mg/kg/day and dose-related, slightly higher levels in bilirubin, glucose, ALT, ALP, total cholesterol, LDL, and HDL at 25 and 100 mg/kg/day in the 4-week study and a slightly higher total cholesterol level at 28 mg/kg/day in the 13-week study.

In rats (males predominantly affected) there was a dose-related increase in incidence of hypertrophy of TSH-producing cells in the pituitary and an increase in incidence and severity of thyroid follicular cell hypertrophy starting at 25 mg/kg/day. These effects are considered secondary to the liver cell hypertrophy, which lead to increased metabolism of the thyroid hormone T4, a well known rat specific effect without relevance for humans. In the 13-week study this hypothesis was supported by the observations of (1) slightly reduced serum T4 levels (but not T3 and TSH) in mainly males, (2) slightly increased T4-glucuronidation activity in liver microsomes, and (3) induction of gene expression of UDP-glucuronyltransferase 2 in the liver.

Other effects in rats were a slight increase in adrenal weight in females at 25 and 100 mg/kg/day and an increased incidence and degree of diffuse vacuolization in the adrenal cortex of males at 100 mg/kg/day.

In rats there were also some minor urinary findings which were considered of equivocal relevance, because of absence of adverse morphological changes in the 4-week study, an equivocal slight exacerbation only of ‘normal’ slight tubular basophilia in the kidney of males at the highest dose in the 13 week study, and absence of up-regulation of any of the known biomarker genes for kidney toxicity (in particular KIM-1).

All the findings in the multiple dose toxicity studies had fully recovered within the 4-week recovery period, with the exception of liver and adrenal weights in female rats, which were still slightly higher than in concurrent controls.
In an oral toxicity study in juvenile rats (highest dose 10 mg/kg/day = MTD) RO4917523
given from post-natal day 7 to 91 induced a decrease in male body weight gain at
≥ 0.5 mg/kg/day and an increase in female food intake at ≥ 2.5 mg/kg/day, behavioral
changes of quantitative components of the functional observational battery (decreased
forelimb grip strength and hindlimb splay) at ≥ 0.5 mg/kg/day, an increase in motor
activity at 10 mg/kg/day, and reduced performance in the learning of path B in the
Cincinnati water maze test (a learning and memory test) at ≥ 2.5 mg/kg/day. These
effects, all considered target pharmacology-related, showed partial or full regression
during the 4-week recovery period or the post recovery observation period. Sexual
maturation and reproductive function were not adversely affected. In view of the
pharmacology-related effects seen at all doses the NOEL was considered
< 0.5 mg/kg/day, and because of absence of adverse effects the NOAEL 10 mg/kg/day.

There were no signs of a genotoxic potential for RO4917523, and there was no
experimental evidence of a direct systemic effect on the immune system.

RO4917523 was phototoxic in vitro (cultured murine fibroblasts), but not in vivo
(hairless rat model), and therefore the risk for inducing a phototoxic skin reaction in man
is considered very low.

In safety pharmacology studies, RO4917523 increased respiration rate in rats
(NOAEL 0.2 mg/kg), increased heart rate (moderate, short lasting) in telemetered
monkeys (NOAEL 10 mg/kg), and decreased gastric emptying and intestinal transit at
≥ 0.1 mg/kg.

In two rat models (Conditioned Place Preference and Intracranial Self Stimulation) for
assessing the reinforcing potential of RO4917523 (doses of up to 3 mg/kg p.o. or i.p.,
respectively) there were no reinforcing effects.

RO4917523 was not teratogenic in the studies on embryo-fetal development in rats and
rabbits.

In fertility studies in rats RO4917523 reduced the mating and fertility indices. These
effects were fully reversible after a treatment-free recovery period of 9 weeks in males
and 4 weeks in females. There were no morphological changes in sexual organs from
both genders. The effect on the mating index was male-mediated (NOEL = 1 mg/kg/day),
while the effect on fertility was female-mediated (NOEL = 0.3 mg/kg/day). In a
combined fertility study (e.g. males and females treated with RO4917523), sperm count
was slightly reduced at 25 mg/kg/day, but sperm motility was normal, whereas in the
4-week general toxicology study with doses of up to 100 mg/kg no effect on either sperm
count or sperm motility was seen.

1.3 Previous Clinical Experience

RO4917523 has been dosed to 233 healthy volunteers in seven clinical studies (a single
ascending dose [SAD] study, a multiple ascending dose [MAD] study, an alcohol
interaction study, three relative bioavailability studies and a drug-drug interaction study)
and to 86 patients in two clinical studies (one study in treatment-resistant depression and
one in Fragile X Syndrome).
1.3.1 Safety

1.3.1.1 Single Ascending Dose (SAD) Study

In the SAD study, single oral doses of 0.25 to 2 mg RO4917523 were administered. Single doses of 0.25 mg and 0.5 mg were well tolerated. Most of the adverse events occurred within 0.5 to 3 hours after administration and were mostly related to CNS (mainly dizziness and somnolence). The number of adverse events (AEs) increased with the dose, particularly at doses above 1 mg (1 AE at 0.25 mg to 29 AEs at 2 mg). The AEs included hypoesthesia/paresthesia, myoclonus, vasovagal malaise (one with, one without loss of consciousness), disturbance in attention and amnesia, gastro-intestinal disorders (nausea, dry mouth), eye disorders (blurred vision, mydriasis), and psychiatric disorders (euphoric mood). Most of the AEs were of mild to moderate intensity but 5 AEs were reported as of severe intensity at the doses of 1.5 and 2 mg (4 cases of dizziness, 1 case of syncope). The dose escalation was stopped at 2 mg due to the occurrence of adverse events of moderate to severe intensity in the majority of the subjects.

1.3.1.2 Multiple Ascending Dose (MAD) Study

During the MAD study, fixed or up-titrated doses of 0.1 mg to 2 mg were administered b.i.d. in the fasted or fed state during 14 days (with the exception of the 0.1 mg b.i.d. cohort in fasted condition that was terminated at Day 8 due to the occurrence of an acute psychotic state, rated as an SAE, and an acute state of anxiety). The most frequently reported AEs affected the ‘central nervous system’, ‘gastro-intestinal system’, and ‘general disorders system’. Dizziness was reported with a higher frequency in the active drug groups (1 to 3 per group of 6 to 9 subjects) than in the placebo group (1 in 15 subjects). Although the exposure levels in this study exceeded those reached in the SAD study, there were no reports of severe dizziness and no clear relationship emerged between the dose and the incidence or intensity of dizziness, suggesting development of tolerance upon repeated dosing. No dose-response relationship emerged either for headache or drowsiness. However, when the drug was given in the fed state, a dose response pattern was suggested for the following neuropsychiatric events: mood (dysphoria, euphoria), cognition (attention and memory, including the cognitive battery results), perception and ideation (hallucinations, paranoid ideation) and sleep (insomnia, nightmares, and hypnagogic hallucinations in up to 38% of the subjects); these events occurred at doses ≥ 1 mg. Such a pattern of dose response was not observed in the fasted state (0.1 and 0.25 mg b.i.d.). All effects resolved within a few days after discontinuation. There were no reports of withdrawal syndrome as assessed by the Rickels withdrawal questionnaire applied from Day 14 until Day 24. In most subjects there were only some single occurrences of abnormalities in the laboratory tests without clinical significance, except one instance of markedly increased ALT whereas Alkaline phosphatase, GGT, total bilirubin and CPK levels were at all times normal leading to the subject’s withdrawal. There were no indication for trends in the vital signs and ECGs compared to placebo.

Interestingly, RO4917523 at 0.25 mg b.i.d was better tolerated when administered in the fed state compared to the fasted state, in particular with respect to psychiatric or CNS adverse events. This was possibly due to the lower exposure to the study drug, measured in this group compared to the corresponding fasted cohort. Indeed Cmax and AUC₀-τ on
Day 14 were respectively 1.8 and 1.6 fold higher in the subjects having received the drug in the fasted state.

1.3.1.3 Single Dose Alcohol Interaction Study

During the Single Dose Alcohol Interaction study, most AEs occurred during the combined treatment with 0.5 mg RO4917523 and 0.5 g/kg alcohol (36 AEs in 19 subjects) followed by treatment with 0.5 g/kg alcohol alone (30 AEs in 14 subjects) and then treatment with 0.5 mg RO4917523 alone (21 AEs in 12 subjects). CNS AEs were more commonly reported under alcohol alone (17), followed by the combined treatment (13) and then RO4917523 alone (7). Gastrointestinal disorders (dry mouth, nausea) were more frequently reported with the combination (8), followed by RO4917523 alone (5). The intensity of these AEs was mostly mild, 6 AEs were recorded as moderate (3 with combined treatment with RO4917523 and alcohol, 2 with RO4917523 alone), 1 with alcohol alone, and none were severe. The 3 AEs of moderate intensity after combined treatment with RO4917523 and alcohol were dizziness, nausea and vomiting. These AEs were resolved without sequelae within 5 minutes. The 3 other AEs of moderate intensity were gastroenteritis, joint dislocation (RO4917523 alone) and headache (alcohol alone) and were considered as unrelated to treatment.

1.3.1.6 Phase 2a Study in Treatment-Resistant Depression

NP22022 was a phase 2a, adaptive fixed dose, randomized, double-blind, parallel-group, placebo-controlled study of the safety and therapeutic effects of RO4917523 in patients with treatment-resistant depression. A total of 46 patients received either placebo, RO4917523 0.1 mg, 0.5 mg, 1.0 mg, or 1.5 mg given once daily with food for 10 days. The unblinded safety data from this study reveal that the treatments were well tolerated. ‘Non-serious’ adverse events and changes in vital signs were not clinically significant, and any changes in laboratory parameters were either not clinically significant or were reversible. Two serious adverse events (suicidal ideation and a suicide attempt) occurred in one patient taking 0.5 mg/day, whose medical history contained similar events.

Based upon some neuropsychiatric events observed in Phase I studies, close attention was given to the reporting of all psychotomimetic adverse events in NP22022. Importantly, no clinically significant changes were reported in a subscale of the BPRS score (including the four items Conceptual Disorganization, Hallucinatory Behavior, Suspiciousness, Unusual Thought Content), confirming the absence of psychotic related events. In addition, no clinically significant changes were reported in the YMRS ‘elevated mood’ item score, confirming that events related to elevation of mood or euphoria have not been observed. Only insomnia, abnormal dreams and nightmares were reported as psychiatric adverse events, allowing us to conclude that the compound has been generally well tolerated in this population.

1.3.1.7 Phase 2a Study in Fragile X Syndrome

NP22578 is an ongoing study in adult patients with Fragile X Syndrome. 40 patients have completed 42 days of treatment with RO4917523 in an outpatient setting (IND 103,917, S-000). The compound was overall well tolerated and safe. One case of auditory hallucinations and one case of catatonia were reported (in the 0.5 mg/day dose cohort); the symptoms were completely resolved after discontinuation without sequelae, and no other psychotomimetic adverse events were observed in the higher dose cohorts of 1.0
and 1.5 mg/day.

1.3.2 Pharmacokinetics

RO4917523 exhibits linear and dose proportional pharmacokinetics after single administration within the dose range of 0.5-2 mg, in fasted condition. The linearity was confirmed in the MAD study where, on the first day, in the fed state, exposure after 0.5 mg b.i.d. was approximately double to that after 0.25 mg b.i.d. When the immediate release formulation is administered maximum plasma concentrations are reached in approximately 1 h (fasted state) to 2-3 h (fed state), and thereafter the concentrations decline in a triphasic manner. The estimate of the terminal elimination half-life by non compartmental analysis is approximately 30-70 hours after single dose and 50-100 hours after reaching steady-state. The compartmental analysis used in the population PK
analysis provides a terminal half-life value of 86 hours in woman and of 62 hours in man in healthy volunteers and depressed patients and an effective half-life value of 69 hours in woman and to 45 hours in man in the same population.

Administration with food decreases peak concentration (C\text{max}) and increases time to peak concentration (T\text{max}) compared to administration in the fasted state. Food had no significant effect on exposure (AUC) calculated after single dose, however higher exposure was noted after multiple b.i.d. administration in the fasted state as compared to fed state (1.7-fold higher AUC\text{0-\tau} on Day 14).

Concomitant alcohol intake had no relevant effect on the exposure of RO4917523, and vice versa.

There is a gender effect on RO4917523 pharmacokinetics; in general exposure is higher in women. In the alcohol interaction study there was 2.4- and 1.4-fold higher AUC\text{last} and C\text{max} values respectively in females compared to males, following a single 0.5 mg RO4917523 dose. There was a trend for higher exposure and longer half-life in females than in males in the multiple dose study. In the relative bioavailability study comparing an optimized formulation of matrix tablet to the reference capsule formulation, AUC\text{last} was estimated as 3.45 times higher in a small sample of 6 females and 15 males. However, considering the entire population of female and male subjects, the population PK analysis estimates the gender effect as AUC female = 1.55 x AUC male.

The strong CYP3A4 inhibitor ketoconazole (single 200 mg dose) had no significant effect on the exposure (C\text{max} or AUC) to a single 0.15 or 0.25 mg dose of RO4917523. In a dedicated drug-drug interaction study ketoconazole 400 mg once daily was given four days prior to a single dose of 0.25 mg RO4917523 and during 14 subsequent days. The exposure ratio was 130% on AUC\text{0-312h} (90% CI = 122-139) and 102% on C\text{max} (90% CI = 94-111). It can be concluded that ketoconazole at steady-state and administered during a large part of RO4917523 elimination phase, had a modest inhibitory effect on RO4917523 clearance.

### 1.3.3 Pharmacodynamics

The effects of RO4917523 on psychomotor and cognitive functions were assessed in healthy volunteers, using computerized psychometric tests batteries, Bond Lader visual analogue scale (VAS), of mood, alertness, and attention (computerized version), and ARCI-49 questionnaire.

- RO4917523 appeared to induce some impairment in the psychomotor and cognitive tests especially in the learning memory test (LMT), body sway, and tests of frontal/executive functions such as choice reaction time (CRT), rapid visual information processing (RVIP), and digit symbol substitution test (DSST). The degree was dose proportional and relatively modest at doses below 1 mg.
- Impairment in cognitive performances noted after single administration of 0.5 mg were not present when this dose was administered repeatedly, indicating the development of tolerance to the effects of RO4917523.
In the MAD study, tests indicative of CNS mediated sedation, such as critical flicker fusion test (CFF) and saccadic eye movement (SEM) did not produce any statistically significant changes compared to placebo except for SEM at the highest tested dose (2 mg b.i.d.) only.

Overall, there was no potentiation of the effects when a 0.5 mg single dose was co-administered with alcohol (0.5g/kg). Additive effects were noted on some CNS parameters, principally assessing sedation and information processing.

There was no evidence of an analgesic effect in the intradermal capsaicin test performed in the MAD study. The low number of control placebo subjects limited the interpretation of the finding.

The effects of RO4917523 on postural stability were assessed in healthy volunteers using body sway tests. In the SAD study, the body sway test revealed an ataxic effect, which was only significant at doses higher than 1 mg and only when the tests were performed with the eyes closed, a condition which amplifies postural imbalance. There was no evidence of an effect of formulation (IR vs. MR) on postural stability.

1.4 Rationale for the Study and Overall Risk-Benefit Assessment

Evidence of the potential benefit of RO4917523 in the treatment of depressive episodes has been substantiated based on: (1) the effect of the compound in preclinical models of depression, (2) the clinically reported antidepressant effect of several agents that modulate the glutamatergic neurotransmitter system (ketamine, riluzole, lamotrigine), and (3) the phenomenological analogy between the side effect profile observed during the phase I studies with RO4917523 and the side effect profile observed with ketamine, particularly on the psychotomimetic events of ideation and perception. The study design rationale can be found in the sections 3.1.1 and 3.1.2. Taking these factors in consideration, the safety of RO4917523 was recently investigated in a study of patients with treatment resistant depression (1.3.1.6) which showed that the medication was overall safe and well tolerated (see study NP22022 in Investigator’s Brochure for additional details).

As previously mentioned, there is a clear unmet medical need to provide more effective therapeutics to patients that have failed to respond to antidepressant treatments which are currently available. In fact, it has been shown that response and remission rates continue to decline with each successive antidepressant treatment in depressed patients [4]. Would it be acceptable to evaluate RO4917523 tolerability in the context of providing a possible resolution of symptoms that is often elusive with conventional therapeutics? Based on the accumulated clinical experience with RO4917523 (up to 1.5 mg/day in patients), Roche considers that the expected benefit for improving the efficacy of treatments in this population outweigh the potential risk associated with this experimental intervention, provided that sufficient safety monitoring is maintained during the study. That is to say, there is a positive benefit-risk assessment to studying the efficacy of RO4917523 in depressed outpatients who have failed to respond to ongoing antidepressant therapy.
2. **OBJECTIVES**

2.1 **Primary Objective**

To evaluate the efficacy of two fixed doses of RO4917523 compared to placebo in a confirmatory manner over 6 weeks as adjunctive therapy in patients with MDD with inadequate response to ongoing antidepressant treatment, based on mean change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

2.2 **Secondary Objectives**

The secondary objectives are to evaluate change after 6 weeks of treatment with RO4917523 versus placebo as adjunctive therapy on the following:

- Clinical Global Impression Scores: Severity (CGI-S) from baseline to end of treatment, and Improvement (CGI-I) at end of treatment
- Safety and tolerability of RO4917523
- Proportion of patients exhibiting remission (a MADRS score of less than or equal to 10)
- Proportion of patients exhibiting response (reduction in MADRS score equal to or greater than 50% of the baseline score)
- Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16)
- Patient Global Impression of Improvement (PGI-I) score at end of treatment

2.3 **Exploratory Objectives**

2.3.1 **Key Exploratory Objective**

To evaluate the effect size (ES) of two fixed doses of RO4917523 compared to placebo over 6 weeks as adjunctive therapy in patients with MDD with inadequate response to ongoing antidepressant treatment, based on mean change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

2.3.2 **Other Exploratory Objectives**

The other exploratory objectives include the investigation of the differential effect of RO4917523 vs. placebo in:

- The proportion of patients who meet MADRS responder criteria plus CGI-I score of 1) “very much improved” or 2) “much improved”
- The proportion of patients who meet MADRS remission criteria plus CGI-I score of 1) “very much improved” or 2) “much improved”
- The speed of onset of antidepressant effect based on change over time in any of the depression symptom scales
- CANTAB Cognitive Test Battery subset
- Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)
- Sheehan Disability Scale (SDS)
2.3.3 Pharmacokinetics
• Pharmacokinetics of RO4917523 in the target population with the objective of performing a population pharmacokinetic analysis with non-linear mixed effect modeling.

2.3.4 Roche Clinical Repository (RCR), Mandatory Biomarker Samples (MBS) and Clinical Genotyping (CG)
Specimens collected for the Roche Clinical Repository (RCR), Mandatory Biomarker Samples (MBS) and Clinical Genotyping (CG) will be used to possibly:
• Identify biomarkers that are predictive of response to RO4917523 treatment
• Increase our knowledge and understanding of the pathogenesis, course and outcome of depression and related diseases
• Develop biomarker or diagnostic assays, and establish the performance characteristics of these assay

See sections 5.7, 5.8 and 5.9 for further information on RCR, MBS and CG sampling.

2.4 Roche Internal Criteria to Advance the Development of RO4917523
For the purpose of internal decision making, Roche may consider to advance the development of RO4917523 if the observed ES is equal to or larger than 0.35 utilizing the LOCF method.

3. STUDY DESIGN
3.1 Overview of Study Design and Dosing Regimen
This is a phase 2, randomized, double-blind, placebo-controlled, parallel-group, multi-center study that will evaluate two fixed doses of RO4917523 versus placebo as adjunctive treatment for six weeks in patients with major depressive disorder with inadequate response to ongoing antidepressant therapy. Patients must have had at least one but no more than three treatment failures (of adequate dose and duration according to the Massachusetts General Hospital Antidepressant Treatment History Questionnaire [MGH ATRQ]); failure to ongoing antidepressant treatment in the current episode is counted as one treatment failure. Further details are provided in section 4.2 Inclusion Criteria.

Following screening procedures to confirm eligibility, patients on ongoing antidepressant therapy will be randomized to one of the three treatment arms: a) RO4917523 0.5 mg, b) RO4917523 1.5 mg, or c) placebo, once daily.

The total duration of the study for each patient will be approximately 2 and a half months, divided as follows:
• Screening Period: up to 14 days
• 6-Week Double-blind Treatment Period
• Follow-up period: 21 days
3.1.1 Rationale for Study Design

This study will include outpatients 18 to 70 years of age with a primary diagnosis of major depressive disorder (MDD) without psychotic features as defined by DSM-IV-TR criteria, and having inadequate response to ongoing antidepressant therapy. To establish a basal level of treatment resistance, the patients must have had at least one (of adequate dose and duration according to the MGH ATRQ) but no more than three treatment failures.

In order to enhance the effect of antidepressant treatments for patients with inadequate response, several clinical strategies are utilized. Note that these strategies may or may not be approved as safe and efficacious by health authorities and should be checked with local regulations before its utilization. They include among others, the addition of a new antidepressant from a different class or mechanism of action, the addition of new generation antipsychotics, potentiation with thyroid hormones, or potentiation with lithium. In this context, this study will help us to understand if RO4917523 added to the ongoing antidepressant medication (SSRI/SNRI only) is efficacious in the treatment of depressive symptoms and if it is safe and well tolerated.

As mentioned, the safety of RO4917523 has been recently investigated in a study of patients with treatment resistant depression (1.3.1.6) showing that the medication was overall safe and well tolerated (see study NP22022 in Investigator’s Brochure for details).

As there is a clear unmet medical need to provide improved therapeutics to these patients, this study aims to investigate the effects RO4917523 in addition to the medication on which the patients have failed to adequately respond. This study will employ a placebo controlled design, in order to minimize the effect that the expectation of receiving an efficacious treatment may have in caregivers and patients alike. Moreover, the adjunctive efficacy of RO4917523 on SSRI or SNRI antidepressant treatment will also be
investigated with this design. It has been determined that patients who have failed to respond after six weeks of antidepressant treatment on SSRIs will achieve remission levels after twelve weeks with the sole continuation of the same antidepressant; in fact, up to 41% of the patients that were initially non-responders and 48% of those who were partial-responders at week six will achieve remission at week twelve [6].

Experimental glutamatergic medications (NMDA antagonists) [2, 7] have been reported to produce a rapid antidepressant effect (e.g., during the first week of treatment) of adequate magnitude (comparable to the mean response reached after six weeks of treatment with available antidepressants) in a population of depressed patients who have previously failed to respond to adequate treatments. We are investigating how quickly and robust an antidepressant effect can be detected or observed once RO4917523 has been initiated within the 42 days timeframe of blinded treatment. This timeframe 1) would allow a determination of the clinical relevance in the efficacy outcome measures, and 2) would also allow the continued characterization of the safety and tolerability profile of RO4917523 in this population.

A 21 day post treatment follow-up period would allow for the duration and persistence of the therapeutic effect to be tracked, as well as to monitor residual adverse events or newly emerging adverse events. This period exceeds five times the effective half-life of RO4917523 (76 hr in woman and 45 hr in man on average, respectively) and even five times the terminal half-life of RO4917523 (93 hr in woman and 63 hr in man on average, respectively) within which 97% of the compound is eliminated following discontinuation.

### 3.1.2 Rationale for Dose Selection

The proposed doses for this study have been selected based on the safety and tolerability observations from the study NP22022 in treatment resistant depression and from the study NP22578 in Fragile X Syndrome, in which doses of RO4917523 ranging from 0.1 mg/day to 1.5 mg/day were studied.

Close attention was given to the reporting of all psychotomimetic adverse events in the NP22022 study, in which 46 patients received either RO4917523 or placebo in an inpatient setting for 10 days. Very importantly, hallucinations, effects on mood (e.g., dysphoria or euphoria), and delusions (e.g., paranoid ideation), were not reported during the study. Only insomnia, abnormal dreams and nightmares were reported as psychiatric adverse events, allowing us to conclude that the compound has been generally well tolerated in this population. Furthermore, no cases of increased psychotic or manic symptoms were reported or detected.

In the NP22578 study in Fragile X Syndrome, 38 patients completed 42 days of treatment with RO4917523 in an outpatient setting. The compound has been overall well tolerated and safe. One case of auditory hallucinations and one case of catatonia were reported in the 0.5 mg/day dose arm; the symptoms were completely resolved without sequelae after discontinuation of the study medication.
Based on the aforementioned clinical experience, and provided that sufficient safety monitoring is maintained, the present study will investigate RO4917523 0.5 mg and 1.5 mg once daily taken in the morning immediately after breakfast as the dosing schedule and regimen.

3.1.3 End of Study
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 patient in the study.

3.2 Number of Patients/ Assignment to Treatment Groups
Approximately 300 patients (100 per treatment arm) will be recruited.

3.3 Centers
The study will be conducted in approximately 60 centers worldwide.

4. STUDY POPULATION
Under no circumstances are patients who enroll in this study permitted to be re-randomized to this study and enrolled for a second course of treatment.

4.1 Overview
The study will include male and female outpatients from 18 to 70 years of age with a primary diagnosis of major depressive disorder (MDD) without psychotic features as defined by DSM-IV-TR criteria, and having inadequate response to ongoing antidepressant therapy. Patients must have had at least one but no more than three treatment failures (of adequate dose and duration according to the MGH ATRQ). Failure to ongoing antidepressant treatment in the current episode is counted as one treatment failure.

4.2 Inclusion Criteria
A patient may be included if the answer to all of the following statements is “yes” at screening, unless otherwise indicated.

General:

1. Male or female, legally adult (minimum 18) up to 70 years of age at time of informed consent
2. Body mass index (BMI) between 18 and 38 kg/m² inclusive
3. Patients with reproductive potential must agree to use contraceptive protection from screening until 21 days after the last dose of study medication as follows:
   a. Males with partners of childbearing potential must use a barrier method of contraception (e.g. condom, diaphragm, or spermicide) or remain sexually abstinent.
   b. Non-lactating, non-pregnant females of child-bearing potential must choose one of the following contraceptive options:
      i. Any one of the following methods: an IUD which was implanted at least 2 months prior to screening, a depot form of medroxyprogesterone, tubal ligation, or male partner surgical sterilization.
ii. Any two of the following methods: oral hormonal contraception, condom, diaphragm or cervical cap plus spermicide, or vaginal sponge.

iii. Remain sexually abstinent.

4. Able and willing to sign a written consent prior to any study related procedures

Neuropsychiatric:

5. A primary diagnosis of major depressive disorder (MDD) without psychotic features as defined by DSM-IV-TR criteria, on the basis of a structured interview (Mini International Neuropsychiatric Inventory [MINI]). The diagnosis of MDD will be confirmed via a central vendor specialized in MDD diagnosis (hereafter referred to as the central vendor) via a computer-administered diagnostic interview (DxV-MDD), when available1.

6. Having inadequate response to an ongoing antidepressant treatment:
   a. Inadequate response defined as having at screening a rater-administered MADRS score of 25 or greater and a CGI-S score of 4 or greater (moderately ill or worse). When available, the computer-administered MADRS score must be 23 or greater. If the above conditions are met, there must also be no more than a 7 point difference between the rater and computer MADRS scores.
   b. Antidepressant treatment defined as pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) of at least 6 weeks duration at the minimum acceptable dose per the MGH ATRQ.

7. Dose and duration of ongoing antidepressant treatment must be verified during the screening period by written documentation which must include one of the following:
   a. Medical records
   b. Pharmacy records
   c. Referral form from treating physician indicating medication, dose, and dates of treatment

8. Having at least one but no more than three antidepressant treatment failures within the current depressive episode. Treatment failure is defined as having inadequate response to an antidepressant treatment of at least 6 weeks duration at the minimum acceptable dose per the MGH ATRQ. The ongoing antidepressant therapy is counted as one treatment failure.

9. Existing medication regimens for other medical conditions should be stable for 6 weeks prior to Baseline, with the intent to remain stable throughout the study (see [4.4] Concomitant Medication below for restrictions).

1 And deemed appropriate according to local medical practices.
4.3 Exclusion Criteria

A patient will be excluded if the answer to any of the following statements is “yes” at screening, unless otherwise indicated.

Treatment history:

1. Currently receiving treatment with a combination of antidepressants (two or more), or on adjunctive or potentiating treatment including antipsychotic agents (typical or atypical), mood stabilizers (anticonvulsants), lithium, triiodothyronine, or stimulants.
2. Previously received RO4917523
3. Enrollment/participation in a clinical trial or intake of an investigational drug within 90 days of screening or 5 times the half life of the investigational drug (whichever is longer)
4. History of failure, or utilization during the current episode of Electroconvulsive Therapy (ECT) or repetitive Transcranial Magnetic Stimulation (rTMS)
5. History of use at any time of Vagus Nerve Stimulation (VNS) or Deep Brain Stimulation (DBS)
6. Planning to begin individual or group psychotherapy during the study. Patients undergoing regular psychotherapy (i.e., at least 90 days duration at the time of screening) are eligible to participate in the study

Diagnosis and psychiatric history:

7. Other current DSM-IV-TR axis I diagnosis. Comorbid anxiety which dominates the clinical presentation or troubles the patient the most is not accepted: Obsessive-Compulsive Disorder (OCD) and Posttraumatic Stress Disorder (PTSD) are specifically not allowed under any circumstances.
8. Current or past history of psychotic symptoms.
9. Current or past history of Bipolar Disorder (e.g., manic, hypomanic, or mixed episodes).
10. Mood disorder due to medical condition or substance use/abuse/dependence.
11. Personality disorder which might interfere with compliance or increase suicidal risk.
12. Alcohol and/or substance abuse/dependence during the last 6 months. Additionally, patients should be advised not to consume alcohol during the duration of the trial.
13. Significant risk of suicide or suicidal behavior, including a history of previous suicide attempts during the current episode, or to develop such a risk during the study.

Past and current other medical history:

14. Other significant or unstable medical condition that could interfere with, or for which the treatment of might interfere with the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the patient in this study, including among others:
   a. Significant or unstable neurological disorder
   b. Unstable or uncontrolled hypertension
c. Hypomagnesemia

d. Abnormal thyroid function. Note that patients under treatment may be allowed
to participate in the study if currently euthyroid and have not had a change in
treatment regime within the last 8 weeks

15. Serology positive for HIV, Hepatitis B or C
16. Clinically significant abnormality on 12-lead electrocardiogram (ECG) at Screening,
including a QTcF equal to or greater than 450 milliseconds
17. Clinically significant laboratory abnormality (note that re-testing is allowed to rule
out potential laboratory errors)
18. For females, pregnancy test positive at screening, breast feeding, or intend to become
pregnant during the course of the trial
19. Positive result for urine drugs of abuse test at screening
20. Hypersensitivity to the excipients of the study drug

Other:
21. Individuals whose occupation is to drive or operate mass transportation (i.e., buses,
trains), large vehicles (i.e., trucks), or heavy machinery.

4.4 Allowed and Prohibited Medication

4.4.1 Ongoing Antidepressant Treatment
Ongoing treatment with a single antidepressant of the SSRI or SNRI class (see inclusion
criteria number 7b and 8) must be continued for the duration of the double-blind
treatment period without modification of the dosing schedule.

4.4.2 Allowed Medications

• Medications used for the treatment of stable medical conditions other than
depression. Existing medication regimens (which may include benzodiazepines)
should be stable for 6 weeks prior to baseline, and with the intent to remain stable
throughout the study.
• Anticonvulsants being utilized for the treatment of epilepsy only of non-
glutamatergic or non-GABAergic mechanism of action (e.g., phenytoin, valproic
acid, carbamazepine).
• For acute anxiety and/or insomnia, a benzodiazepine (up to 2 mg/day lorazepam,
or equivalent), or a non-benzodiazepine hypnotic (immediate release zolpidem up
to 10 mg, controlled release zolpidem up to 12.5 mg, or zaleplon up to 10 mg, at
bedtime) can be utilized. Use of any one of these agents should be prescribed on
an as needed basis only, and limited to no more than three days per week, and not
within 8 hours of any visit. Use of alternative agents may be allowed after
consultation with the Sponsor/Medical Monitor.
4.4.3 Prohibited Medications

All other psychotropic medications (with the exception of those allowed in 4.4.1) are prohibited starting two weeks before randomization (or a period equivalent to 5 half lives for that medication, which ever is longer). These include:

- Fluvoxamine
- Non-SSRI or non-SNRI antidepressants (including St. John’s Wort)
- Antipsychotics
- Psychostimulants
- Lithium
- Thyroid hormone used for antidepressant potentiation
- Opioid analgesics
- Anticonvulsant medications utilized as mood stabilizers, adjunctive, or potentiating antidepressant treatment
- GABAergic drugs including: tiagabine, vigabatrin, baclofen, pregabalin and gabapentin
- Glutamatergic drugs including: riluzole, topiramate, memantine, lamotrigine
- Herbal supplements
- Omega-3 fatty acids (i.e. fish oil and flaxseed oil)
- Magnesium supplements
- Dextromethorphan
- All other psychotropic drugs

4.5 Criteria for Premature Withdrawal

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

In the case that the patient decides to prematurely discontinue study treatment [“refuses treatment”], he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the CRF. If lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made with an explanation of why the patient is withdrawing from the study.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the investigator without the patient’s consent. The investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is felt by the investigator that it is in the best interest of the patient to be terminated from the study. In particular, the investigator should consider withdrawing a patient due to ‘lack of response with persistence of unpleasant symptoms’ if such symptoms are deemed unsafe or intolerable by the investigator or the patient. Any administrative or other reasons for withdrawal must be documented and explained to the patient.
The investigator may also withdraw a patient in case of evidence of suicidal ideation, behavior or risk revealed by the Columbia-Suicide Severity Rating Scale (C-SSRS) at any time during the study. A confirmed positive finding on the C-SSRS, as defined in section 5.5.4.3 (e.g., a “yes” to question 4, indicating suicidal ideation with intention to act), will warrant discontinuation of the patient from the study. The reasons for withdrawal must be documented and explained to the patient.

In addition, as an additional safeguard, according to the FDA’s “Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation” (June 2009), discontinuation of treatment should be considered if patients exceed the following liver function test threshold values:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (Serum Total Bilirubin >2xULN or INR >1.5)*
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)*.

*Note that if ALT or AST >3xULN, the investigator should perform INR testing via local lab to ensure that the threshold condition is comprehensively assessed.

Whether the decision to discontinue is made by the patient or by the investigator, an accurate and detailed description of the reason for discontinuation should be captured in the eCRF. If the reason for removal of a patient from the study is an Adverse Event, the principal specific event will be recorded on the eCRF. The patient should be followed until the Adverse Event has resolved, if possible.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible. If a patient withdraws from the study early, an attempt should be made to complete all study assessments listed under End-of-treatment in the Schedule of Assessments Section 5, on the last day of study medication dosing or as soon as feasible after that.

4.5.1 Withdrawal Of Patients From the Roche Clinical Repository (RCR)

Patients who gave consent to provide RCR specimens have the right to withdraw their specimen from the RCR at any time for any reason. If a patient wishes to withdraw his/her consent to the testing of his/her specimen(s), the investigator must inform the Roche monitor in writing of the patient’s wishes using the RCR Subject Withdrawal Form and enter the date of withdrawal in the patient’s Case Report Form (CRF). A patient withdrawal from the main trial does not, by itself, constitute withdrawal of the specimen from the RCR, likewise a patient withdrawal from the RCR does not constitute a withdrawal from the main trial.
4.6 Replacement Policy [Ensuring Adequate Numbers of Evaluable Patients]

4.6.1 For Patients
Patients discontinued from the study after randomization for any reason will not be replaced.

4.6.2 For Centers
A center may be replaced for the following administrative reasons:

- Excessively slow recruitment
- Poor protocol adherence
- Non-compliance with GCP or any significant audit findings
- Administrative decision made by the sponsor.

New centers may also be added during the course of the study.

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 1 Schedule of Assessments

<table>
<thead>
<tr>
<th>Visit Name/Study Week</th>
<th>Screening</th>
<th>Day 1(^1) (baseline)</th>
<th>Day 3</th>
<th>Day 7 (Wk 1)</th>
<th>Day 11 telephone call only</th>
<th>Day 14 (Wk 2)</th>
<th>Day 21 (Wk 3)</th>
<th>Day 28 (Wk 4)</th>
<th>Day 35 (Wk 5)</th>
<th>Day 42(^3) (End-of-treatment)</th>
<th>Day 63 (Follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window (days)</td>
<td>≤ 14 days prior to baseline</td>
<td>N/A</td>
<td>+1 day</td>
<td>+/- 1</td>
<td>+/- 1</td>
<td>+/- 2</td>
<td>+/- 2</td>
<td>+/- 2</td>
<td>+/- 2</td>
<td>+/- 2</td>
<td>21 +/- 3 days after 'end of treatment'</td>
</tr>
</tbody>
</table>

Informed Consent X
Inclusion/Exclusion criteria X
ATRQ X
DxV-MDD\(^2\) X
Medical and psychiatric history (incl. MINI) X
Physical Examination\(^3\) X
12 lead ECG\(^4,5\) X
Weight X
Vital Signs\(^6\) (BP, HR, Temp) X X X X X X X X X
Blood Chemistry X X X
Hematology X X X
UrimalYSIS/ менстрual status X X X
Urine drug screen X X
Virology X
Pregnancy Test X X
PK Samples X\(^9,10\) X\(^9\) X\(^9\) X\(^9\) X\(^9\) X\(^9\) X\(^9\)
Optional RCR sampling- inherited X
Optional RCR sampling- non inherited X
Mandatory biomarker sampling X

\(^1\) Telephone call only
\(^2\) DxV-MDD
\(^3\) Include all visits
\(^4\) Include all patients
\(^5\) Include all patients
\(^6\) Include all patients
<table>
<thead>
<tr>
<th>Visit Name/Study Week</th>
<th>Screening</th>
<th>Day 1(^{1}) (baseline)</th>
<th>Day 3</th>
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<th>Day 28 (Wk 4)</th>
<th>Day 35 (Wk 5)</th>
<th>Day 42 (^{2}) (End-of-treatment)</th>
<th>Day 63 (Follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window (days)</td>
<td>&lt; 14 days prior to baseline</td>
<td>N/A</td>
<td>+1 day</td>
<td>+/- 1</td>
<td>+/- 1</td>
<td>+/- 2</td>
<td>+/- 2</td>
<td>+/- 2</td>
<td>+/- 2</td>
<td>+/- 2</td>
<td>21 +/- 3 days after ‘end of treatment’</td>
</tr>
</tbody>
</table>

**Clinical Genotyping sampling**

- X

**CANTAB**

- X

**MADRS\(^{3}\)**

- X

**CGI-S**

- X

**CGI-I**

- X

**PGI-I**

- X

**C-SSRS\(^{5}\)**

- X

**QIDS-SR16**

- X

**Q-LES-Q-SF**

- X

**SDS**

- X

**Prior and Concomitant Treatments**

- X

<table>
<thead>
<tr>
<th>Adverse Events(^{13})</th>
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<th>X</th>
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</thead>
<tbody>
<tr>
<td>BPRS (sub-scale)</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<td>YMRS (item 1)</td>
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<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Drug Dispensation and Return**

- X

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1. All baseline assessments must be conducted within 24 hours and prior to administration of the first dose of study medication.

2. Patients will complete the DxV-MDD computer-administered diagnostic interview prior to the MINI, when available.

3. A complete physical examination will be performed at screening and week 6 (end-of-treatment).

4. Height will be collected only at screening.

5. 30 minutes should elapse between the last venipuncture and the measurement of vital signs and ECG. ECG is conducted after remaining in the semi supine position for at least 10 minutes.

6. All ECGs will consist of three consecutive interpretable ECG recordings (as close as possible, and not more than 2 minutes apart).

7. In addition to the rater-administered MADRS, the MADRS assessment will also be completed by the patient via a computer supplied by a central vendor, when available. The central vendor will be blinded to study treatment. The rater’s MADRS score will be entered onto the central vendor’s computer system.

8. If double-blind treatment is discontinued early, the ‘end-of-treatment visit’ should be performed as soon as possible (“early discontinuation visit”). One PK sample will be taken at any time during the “early discontinuation visit.” A ‘follow-up visit’ should be conducted 21 days afterwards and no PK sample taken.

9. The ‘C-SSRS baseline’ will be administered at screening. The ‘C-SSRS since last visit’ will be administered at subsequent visits (including the baseline).

10. At these visits, PK sampling performed at 0 (pre-dose) and 4 hours (according to patient availability). At these visits, an additional PK sample performed at 6 hours (according to patient availability).
Table 1 | Schedule of Assessments (Cont.)

11). PK sample drawn anytime.
12). The CANTAB at screening is administered to patients with confirmed eligibility (pending only laboratory results).
13). After informed consent, but prior to initiation of study medication (i.e. during screening), only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures).

5.1 | Screening Period

5.1.1 | Informed Consent Form (ICF)

All patients must sign and date the most current IRB/IEC-approved written informed consent before any study specific assessments or procedures are performed. Documentation of informed consent must be kept in the patients’ study medical records. The original informed consent document will be retained by the investigator.

5.1.2 | Screening

The study center will access an Interactive Voice Response System/Interactive Web Response System (IVRS) to register the patient into screening. Screening procedures should be performed within a period of time not exceeding 14 days (see required assessments in Table 1). The screening period may be extended by the PI in consultation with the Sponsor/Medical Monitor.

Patients who fail to meet eligibility criteria may be screened again at a later date after consultation with the Sponsor/Medical Monitor.

Once all inclusion and exclusion criteria are met, an Eligibility Screening Form/Eligibility Assessment Form (ESF/EAF) is completed by the investigator and sent to the Sponsor/Medical Monitor for approval of the patient to participate in the study. The Sponsor/Medical Monitor will confirm the patient’s eligibility in IVRS and notify the site.

A screen failure log must be maintained by the investigator.

5.2 | Procedures for Randomization of Eligible Patients

In order to be enrolled into the double-blind treatment period, patients must have:

- No significant risk of suicidal behavior (e.g., consider the Suicidal Ideation section of the C-SSRS “Since Last Visit” for this evaluation)
- No significant change in medical or psychiatric condition, or change in medications since screening (as agreed with the Sponsor/Medical Monitor when appropriate)
- Negative result on the Baseline pregnancy test (if applicable)
- No change in ongoing antidepressant therapy, and the ability to continue for the duration of the double-blind treatment period without modification to the dosing schedule
- An EAF approved by the Sponsor/Medical Monitor
The Double-blind Treatment Period begins with the investigational site call into IVRS confirming the patient’s eligibility as per the ESF/EAF. The patient will be randomized and receive their first dose of study medication on Day 1.

The patient randomization numbers will be generated by Roche or its designee. The treatment allocation will be stratified by geographical region/country, as follows: Europe, United States, Latin America, Asia (excluding Japan) and Japan.

The patient randomization numbers are to be allocated sequentially in the order in which the patients are enrolled according to the specification document agreed with the IVRS vendor. A patient Enrollment and Identification Code List must be maintained by the investigator.

5.3 Double-blind Treatment Period

Dose 1 of the blinded study medication is to be administered in the clinic immediately after a meal and before 12 pm (noon), or soon thereafter upon consultation with the Sponsor/Medical Monitor, once all baseline procedures and assessments (Table 1) are completed. Patients will remain at the clinic for 6 hours after the first dose for safety monitoring and for the PK samples (according to clinical observation and patient availability). Subsequently, dosing will be once daily in the morning immediately after breakfast.

As with any experimental drug at this stage of development, it is advisable for patients not to drive or operate dangerous machinery until known side effects (e.g., dizziness and somnolence) can be adequately assessed on an individual basis during the trial.

At Day 11, telephone contact with the patient by a clinician is required to monitor for the emergence of any clinically significant adverse events.

Patients will arrive at each study visit without having taken their daily dose of study medication, and site staff will record the time of their last dose. Following collection of the pre-dose PK blood sample (if applicable) and a meal, patients will take their next dose of study medication before 12 pm (noon) or soon thereafter upon consultation with the Sponsor/Medical Monitor. The last dose of study medication will be administered on Day 42 (End-of-Treatment visit).

5.4 Follow-up Period

A single Follow-up visit will be performed 21 days after the End-of-Treatment visit (see Table 1). During the follow-up period, adjustments to antidepressant treatments may be initiated if deemed necessary by the investigator.

5.5 Clinical Assessments and Procedures

5.5.1 Rater Selection and Training

To be considered as a rater in this study, a member of the site staff must be a physician, a nurse with certifiable psychiatric practice, or a clinical psychologist. Qualified nurses and clinical psychologists must have a minimum of two years experience administering standardized rating scales. (participation of raters with different qualifications should be agreed upon with the Sponsor/Medical Monitor on a case by case basis).
Raters may be trained and certified on the clinician-administered scales and a quality monitoring program may be implemented to ensure rating consistency during the trial.

5.5.2 Assessments for Eligibility

5.5.2.1 Detailed psychiatric history

A detailed psychiatric history will be taken during the screening period. This will include documentation of previous treatment for major depression and medication regimens and changes. Previous psychiatric hospitalizations and out-patient treatment should also be noted.

5.5.2.2 Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH ATRQ)

The MGH ATRQ is a patient-completed instrument used to determine treatment resistance in major depressive disorder [8, 9]. A clinician may assist the patient to complete the instrument. The MGH ATRQ defines 6 weeks on a minimally acceptable dose of antidepressant medication as an adequate treatment duration. As noted in Inclusion criterion number 7, information regarding the ongoing antidepressant treatment must be verified by way of written documentation.

5.5.2.3 Medical history and Physical examination

The patient’s medical history will be taken during the screening period. A complete physical exam will be performed at screening and Week 6. The patient’s height will be recorded at screening only.

For pre-menopausal females, menstrual status will be recorded at each visit when a urine sample is collected.

5.5.2.4 Computer-Administered Diagnostic Interview

Patients will be instructed to complete a computer-administered diagnostic interview (DxV-MDD) at the screening visit, when available. The DxV-MDD will collect data about the subjects’ history relative to lifetime history of MDD. Each site will be provided with a laptop computer that will record the subject’s responses to the computerized questionnaire. Each site will receive training on the use of the laptop and perform a secure data transmission test with the central vendor.

After the screening visit, the site will transfer the information collected by the laptop through a secure, encrypted sFTP connection. The subject’s responses will be evaluated by independent clinical experts at the central vendor. The details of the subject’s history will be evaluated by an independent MDD expert based on the responses to the computerized interview. To establish confidence in the diagnosis, any diagnostic uncertainty raised by the patient’s responses to the diagnostic interview must be resolved by the Investigator, in collaboration with a central vendor clinician. Patients for whom diagnostic agreement between the Investigator and the central vendor cannot be reached may not be considered appropriate for study participation².

² If deemed appropriate according to local medical practices.
5.5.2.5  Mini International Neuropsychiatric Inventory (MINI)

In order to verify a diagnosis of major depressive disorder (MDD) without psychotic features for inclusion in this study (and other related inclusion criteria), the patient will be evaluated by use of the MINI [10] during the screening period. The MINI is a short, structured diagnostic interview designed to provide psychiatric diagnoses according to the DSM-IV and ICD-10 criteria. Thus it was intended to serve as a tool that could be applied internationally in such settings as multicenter clinical trials.

5.5.3  Efficacy

The collection of efficacy assessments is detailed in the Schedule of Assessments [Table 1].

5.5.3.1  Montgomery Asberg Depression Rating Scale (MADRS)

The MADRS [11] was designed to assess the overall severity of depressive symptoms in patients with major depressive disorder. The scale is also intended to be sensitive to treatment effects and to discriminate between medication versus placebo. The MADRS is a 10-item instrument. Items are rated on a scale of 0 to 6 with anchors at 2-point intervals; hence the total score ranges from 0 to 60. To improve the quality and consistency of the MADRS ratings across study centers, the MADRS-SIGMA (an interview guide which provides structured probes) will be utilized [12]. See Appendix [Appendix 3] for details.

This study will utilize a rater quality control system conducted by a central vendor, blinded to study treatments. The rater quality control system allows the study team to monitor the primary outcome measure at treatment phase assessments in the study and give ongoing feedback and remediation to the rater in the study, when necessary.

Each study site will be provided with a laptop computer containing the quality control system software, receive training on use of the laptop, and perform a secure server connection test with the central vendor. The rater will administer the MADRS to the subject per protocol procedures. The rater’s MADRS scores will be entered onto the laptop computer. Afterwards, the subject will complete an interactive interview on the computer (i.e., the computer-administered MADRS). The interview involves a series of probe and follow up questions with multiple choice response options (mean time for completion is < 10 minutes). Subjects will not be required to type any responses.

The subject responds to computer prompts presented. The laptop is not connected to the Internet during the interactive interview. The quality control system software restricts the user’s access to only the subject-user interface. The quality control system software places an unalterable time and date on each report which cannot be modified (meets requirement 21 CFR Part 11). The study assigned subject ID number is the only identifying information that is stored into the laptop computer and transmitted to the vendor; therefore, the vendor will be blinded to the study treatment.

After the subject’s visit, the site will transfer the information collected by the laptop through a secure, encrypted FTP connection (meets requirement 21 CFR Part 11). The transfer will be acknowledged to the site on the laptop screen. The information is stored on a password protected server that restricts access to registered users or IP addresses.
After the transfer, the information is analyzed by the vendor’s quality control system software. The vendor examines the subject’s interview responses and quality control system software ratings in parallel with the rater’s outcome measure scores and compares the two for consistency. If an individual report falls outside the study thresholds, the central vendor may schedule a structured review with the site rater to determine probable sources of the discordance. If a review is necessary, the central vendor will contact the site within five business days. The rater’s assigned scores are not altered by the review or any exchange with the central vendor. The central vendor will apply the same methodology for review at each study visit.

The rater quality control system maintains an ongoing performance profile for each rater. Quality issues are evaluated and corrected continuously throughout the study. Reports are updated continuously and available to the study team.

### 5.5.3.2 Clinical Global Impression- Severity (CGI-S) and Improvement (CGI-I)

The CGI rating scales are tools used to evaluate both the severity of illness and change from baseline [13]. The CGI-S reflects the clinician’s impression of the patient’s current illness state on a 7-point scale ranging from no symptoms (1) to very severe (7). The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point scale, ranging from very much improved (1) to very much worse (7). In this study, overall clinical status will be evaluated with the CGI-S and CGI-I. See Appendix 4 for details.

### 5.5.3.3 Patient Global Impression of Improvement (PGI-I)

The PGI-I is a self-reported instrument to record the patient’s own assessment of improvement since baseline. The patient is asked to rate their condition as compared to before they began study medication using a 7-point scale, ranging from very much better (1) to very much worse (7). The PGI-I is essentially a patient-reported version of the CGI-I. See Appendix 5 for details.

### 5.5.3.4 Cambridge Neuropsychological Test Automated Battery (CANTAB®)

Cognitive performance will be assessed using the CANTAB® computerized battery provided by Cambridge Cognition™. The main cognitive domains known to be impaired in depression include memory, attention, executive function and speed of processing. A subset of the CANTAB® tests will be used to assess function in these domains: Motor Control Task (MOT), Rapid Visual Processing (RVP), Delayed Match to Sample (DMS), Emotional Recognition Task (ERT), -10 min break-, Paired Associates Learning (PAL), the Stockings of Cambridge (SOC, at screening) or the One-Touch Stockings of Cambridge (OTS, at subsequent visits), and Attention Shifting Test (AST).

During the screening period, the CANTAB battery will be administered to patients with confirmed eligibility (pending only laboratory results).
5.5.3.5 **Quick Inventory of Depressive Symptomatology Self Report- 16 item version (QIDS-SR16)**

The QIDS-SR16 [14, 15] was designed to assess the severity of depressive symptoms in a self-rated format. The scale assesses all of the symptom domains selected by DSM-IV to diagnose a major depressive episode. Each of the 16 items is scored on a 4-point anchored scale, representing least severe (0) to most severe (3). Specific instructions for calculating a total score are included in the scale. See Appendix 6 for details.

5.5.3.6 **Quality of Life Enjoyment and Satisfaction Questionnaire- Short Form (Q-LES-Q-SF)**

The Q-LES-Q-SF [16] was developed to measure the degree of enjoyment and satisfaction experienced in various areas of daily life in a self-rated format. The instrument is intended to detect differences among groups of patients, as well as individual patients over time. The full version of the Q-LES-Q consists of 60 items, however the 16-item short form version will be utilized for this study. See Appendix 7 for details.

5.5.3.7 **Sheehan Disability Scale (SDS)**

The SDS [17] is a combination of three self-rated items designed to measure the extent to which three major areas of a patient’s life are impaired by panic, phobic, anxiety, or depressive symptoms. The scale was developed as an outcome measure that would be sensitive to change and to differences over time when evaluating medication treatment versus placebo. The patient rates the extent to which his or her 1) work or school, 2) social life or leisure activities, and 3) home life or family responsibilities have been impaired by symptoms, using a 10-point visual analog scale. See Appendix 8 for details.

5.5.4 **Safety**

The safety and tolerability of RO4917523 will be assessed by monitoring vital signs, laboratory tests, ECGs, the emergence of symptoms/adverse events of interest and other adverse events as detailed in the Schedule of Assessments [Table 1]. For additional safety instructions and guidance, including Adverse Events (AEs) & Laboratory Abnormalities and Handling of Safety Parameters, refer to Section 7.

5.5.4.1 **Brief Psychiatric Rating Scale (BPRS)**

A subscale (4 items) of the BPRS [18] will be completed only to follow up on treatment emergent psychotic-related and mania-related (mania or hypomania) adverse events. The symptom constructs included are conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. See Appendix 9 for details.

5.5.4.2 **Young Mania Rating Scale (YMRS)**

The YMRS [19], item 1 only for mood elevation will be completed only to follow up on treatment emergent psychotic-related and mania-related (mania or hypomania) adverse events. See Appendix 10 for details.
5.5.4.3 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool used to assess the lifetime suicidality of a patient (C-SSRS baseline) as well as any new instances of suicidality (C-SSRS since last visit). The C-SSRS incorporates a structured interview to prompt recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality. A validated, self rated version of the C-SSRS, the eC-SSRS [20] will be used to capture these data via an interactive voice response telephone system. The eC-SSRS baseline version will be administered at screening and the C-SSRS since last visit version will be administered at subsequent visits, including the baseline visit (see [Table 1]). Training will be provided on the administration of the C-SSRS rating scale, and on the eC-SSRS system for patient use.

eC-SSRS Administration: During a visit, patients will be directed to a private, quiet place with a telephone to complete the assessment. This assessment should be conducted early in the visit to provide sufficient time for the report to be received at the study site prior to patient departure. At the conclusion of each assessment, the site will receive an eC-SSRS Findings Report via e-mail or fax. The report presents the findings for suicidal ideation, intensity of ideation, suicidal behavior, and lethality/medical damage (for actual suicide attempts only).

Positive reports are generated for ANY of the following findings:

- Suicidal ideation with intention to act
- Suicidal ideation with specific plan and intent
- Made suicide attempt
- Interrupted suicide attempt
- Aborted suicide attempt
- Preparatory behaviors for making a suicide attempt

Negative suicidality indication reports are generated when there are NO indications of the above.

Positive Findings: Should the system report that the patient has a positive suicidal indication, the site will be immediately notified by a telephone call from the vendor, as well as by fax / email. The site staff should take appropriate steps to interview the patient, e.g. complete a clinician administered C-SSRS. Depending on the results of the interview, the patient may be referred to a psychiatrist for a follow-up evaluation. The patient should not be released from the evaluation site until it is confirmed that the call is complete, the report is reviewed and the patient is not considered to be at risk. Ultimately, the determination of suicidality and risk is up to the evaluation site’s clinical judgment.

Suicidality Monitoring Data: The eC-SSRS Findings Report will remain at the evaluation site as source data and the data will be sent by the vendor electronically for inclusion in the database. Any clinician administered C-SSRS will be kept at the site as source data and entered into the eCRF.
5.5.4.4 Vital Signs and weight
Vital signs including BP and pulse will be recorded in the supine position after resting 3 – 5 minutes, and in the standing position after 2 minutes. The same arm should be used for all BP measurements. Vitals should be measured either prior to or no less than 30 minutes after the last blood draw.

Weight will be measured at the time points specified in [Table 1].

5.5.4.5 ECG
Twelve lead ECG measurements (indicated in [Table 1]) will be performed in the supine position and will consist of three interpretable recordings (performed as close as possible, not more than two minutes apart). ECGs will be interpreted by cardiologists using a centralized ECG vendor. Procedures are described separately in the ECG manual. The investigator or designated qualified clinician must review, sign, and date the reports. All ECG results will be electronically loaded into the study database.

ECG should be measured either prior to or no less than 30 minutes after the last blood draw.

5.6 Laboratory Assessments
Laboratory assessments (blood and urine samples) will be collected at the time points specified in [Table 1] and analyzed by a central laboratory. Parameters to be analyzed are shown below:

- Chemistry: magnesium, sodium, potassium, bicarbonate, chloride, urea (BUN), serum creatinine, fasting glucose, calcium, total protein, serum albumin, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, total cholesterol, triglycerides, Free T4 and TSH. FSH and estradiol will be measured in females if clinically appropriate to confirm post-menopausal state.

- Hematology: hemoglobin, hematocrit, erythrocytes (RBC), leukocytes (WBC), platelets, differential (counts): neutrophils, eosinophils, and lymphocytes

- Virology: Hepatitis B, Hepatitis C and HIV (screening only)

- Urinalysis: Midstream urine sample collected and analyzed by dipstick for pH, glucose, blood, and protein. If there is clinically significant positive result, urine will be sent to the central laboratory vendor for microscopy and culture.

- Pregnancy test: Female patients of childbearing potential will undergo urine pregnancy tests (analyzed by dipstick).

- Drugs of Abuse: Urine samples will be analyzed for the presence of the following drugs: amphetamine, cannabinoids, opiates, cocaine, barbiturates, PCP.
The total volume of blood loss for laboratory assessments will be approximately 139 mL.
(including volume collected for PK sampling, MBS, CG and optional RCR samples).

The samples for this study should be classified, packed and shipped as UN3373 Biological Substance, Category B.

5.6.1 Pharmacokinetic [PK] Assessments

Blood samples for population pharmacokinetic determinations of RO4917523 will be collected, based on patient availability, as specified in the Schedule of Assessments and Schedule of PK Sampling (Table 1 and Table 2).

Plasma concentrations will be measured by a specific and validated LC/MS/MS method.

Up to 11 samples (2 mL each) for each patient will be collected during the study. The procedures for the collection, handling and shipping of laboratory samples will be provided in the Sample Collection, Handling and Logistics Manual.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Pre-dose</th>
<th>4h Post-dose</th>
<th>6h Post-dose</th>
<th>Any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Day 14</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 42 (end-of-treatment)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Day 63 (follow-up/early withdrawal)</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

Patients will take their medication at the study centre on all study visit days and in particular on PK visit days.

For all patients who withdraw before completion of the double-blind treatment, one PK sample will be taken at any time during the early discontinuation visit. The date and time of the last dose of study medication should be recorded in the eCRF.

To ensure that evaluable data are collected for each patient, PK samples must be taken at the time points stated in Table 2 or as close to these time points as possible. On the day of PK assessment, the following will be recorded onto the eCRF:

- the actual date and time of dosing on the PK day
- the actual date and time of dosing on the two preceding days
- the actual time of meal in relation to dosing on PK day
- the actual date and time of PK sampling.

Reasons for missed PK samples or those taken late in error must be provided and the actual sampling time recorded in the eCRF.
5.7 Roche Clinical Repository Specimen(s)

Specimens for dynamic (A. non inherited) biomarker discovery and validation will be collected from consenting patients and where permissible with local regulations. These specimens will be used for research purposes to identify dynamic biomarkers that are predictive of response to RO4917523 treatment (in terms of efficacy-dose, safety and tolerability) and will help to better understand the pathogenesis, course and outcome of depression and related diseases. To these ends analysis may include determination of markers of synaptic plasticity and glutamate signaling. Specimens for dynamic biomarker discovery will be single coded like any other clinical sample (labeled and tracked using the patient’s study identification number- see Section 17).

Specimens for genetic biomarker (B. inherited) discovery and validation will also be collected from consenting patients and where permissible with local regulations. The pharmacogenetic information gathered through the analysis of specimens in the Roche Clinical Repository (RCR) is hoped to improve patient outcome by predicting which patients are more likely to respond to specific drug therapies, predicting which patients are susceptible to developing adverse side effects and/or predicting which patients are likely to progress to more severe disease states. Such genetic samples collected for analysis of heritable DNA variations will be double coded: a new independent code will be added to the first code to increase confidentiality and data protection (see Section 17).

The results of specimen analysis from the RCR 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.

All RCR specimens will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The specimens in the RCR will be made available for future biomarker research towards further understanding of treatment with RO4917523, of depression, related diseases and adverse events, and for the development of potential associated diagnostic assays. The implementation and use of the RCR specimens is governed by the Roche Clinical Repository policy to ensure the appropriate use of the RCR specimens.

5.7.1 Specimen Types

The biomarker sampling below is optional. Samples will be stored for exploratory analysis after the end of the study.

A. Non-inherited: 1. Plasma and serum at baseline and end of treatment = 4 samples

2. RNA at baseline and end of treatment = 2 samples

3. DNA at baseline and end of treatment for epigenetics = 2 samples

B. Inherited: 4. DNA at baseline for genetics = 1 sample
1. Plasma / Serum assays

Blood samples for plasma and serum isolation will be obtained at baseline and the end of treatment as shown in Table 1. A total of 4 samples (2x6 mL for plasma and 2x6 mL for serum; 24 mL total) for each patient will be collected during the study. These samples will be used for biomarker assays for candidate depression biomarkers. For sampling procedures, storage conditions and shipment instructions see study Sample Collection, Handling and Logistics Manual.

2. Blood for RNA expression profiling

Blood samples (2 x approximately 2.5 mL collected in PAXgene vacutainers) for RNA isolation will be collected at baseline and the end of treatment as shown in Table 1 (10 mL total). The samples may be tested using techniques such as a micro array profiling system and / or RT PCR to study the expression profile of genes known to be involved with depression and any other differentially expressed genes relative to treatment response, dose response or re-treatment. For sampling procedures, storage conditions and shipment instructions see study Sample Collection, Handling and Logistics Manual.

3. Blood sample for epigenetic analysis

Blood samples (approximately 6 mL in K3 EDTA) for DNA isolation will be collected at baseline and the end of treatment as shown in Table 1 (12 mL total). The sample may be processed using techniques to identify epigenetic modifications such as DNA methylation microarray profiling. See study Sample Collection, Handling and Logistics Manual for more details.

4. Blood sample for genetic analysis

A single blood sample (approximately 6 mL in K3 EDTA) for DNA isolation will be collected as indicated in Table 1. If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected at any time (after randomization) during the conduct of the clinical study. The sample may be processed using techniques such as sequencing or microarray profiling. See study Sample Collection, Handling and Logistics Manual for more details.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the case report form (CRF) and/or in the clinical database.

5.8 Mandatory Biomarker Sampling (MBS)

Blood samples for serum and plasma protein biomarker discovery and validation (such as, but not limited to, neurotrophic factors or cytokines) will be collected from all patients where permissible with local regulations at baseline and the end of treatment as indicated in Table 1. A total of 4 samples (2x6 mL for serum and 2x6 mL for plasma; 24 mL total) for each patient will be collected during the study. Specimens will be used for research purposes to identify or validate dynamic protein biomarkers that may be predictive of response to RO4917523 treatment (in terms of dose, safety and tolerability) or contribute to the pathogenesis, course and outcome of depression and related diseases. These specimens will be destroyed no later than 5 years after the end of the study. See study Sample Collection, Handling and Logistics Manual for more details.
5.9 Clinical Genotyping

A 3 mL whole blood sample will be taken for DNA extraction from all patients where permissible with local regulations at baseline as indicated in Table 1. The DNA will be used to explore whether genetic variants are related to the pharmacokinetic / pharmacodynamic behavior, or observations on the safety and efficacy of RO4917523 or the ongoing antidepressant medication for one or more of the following specific genes: the cytochrome P450 variant 1A2 gene (CYP1A2), the metabotropic glutamate receptor 5 (GRM5), the serotonin 2A receptor (HTR2A), the serotonin transporter (SLC6A4), and brain derived neurotropic factor (BDNF). Data arising from this analysis will be subject to standard confidentiality and data protection. This specimen will be destroyed immediately after the analysis has been completed. See study Sample Collection, Handling and Logistics Manual for more details.

6. Investigational Medicinal Product

For the purposes of this study, the Investigational Medicinal Product (IMP) is defined as the supplied dosage form of RO4917523 or matching placebo provided during the randomized treatment period. Ongoing treatment with antidepressant medication of the SSRI or SNRI class is not considered IMP and will not be supplied.

6.1 Dose and Schedule of IMP

The first dose of study medication (RO4917523 0.5 mg, RO4917523 1.5 mg, or placebo) will be on Day 1, after all baseline assessments and pre-dose PK sampling have been conducted, and after a meal. Study medication will be administered once a day in the morning immediately after breakfast. Each dose will consist of two capsules.

6.1.1 Dose Modifications, Interruptions and Delays

If the patient accidentally or by intention consumes more of the study medication than directed they should be instructed to notify their PI immediately, who will in turn evaluate and implement the appropriate clinical care strategy necessary.

If dose schedule needs modification, prior approval of the sponsor/Medical Monitor should be obtained. This should be appropriately documented and every effort taken to assure the time of dosing be as consistent as possible for the duration of the study.

If patient accidentally forgets to take the medication, they should be instructed to inform the site PI who in turn may recommend the following schedule:

- If before 12 pm (noon) of the same day of the missing dose, instruct the patient to take the medication with food.

- If after 12 pm (noon) the same day of the missing dose, instruct the patient not to take the medication that day. The treatment will be reinitiated the next day according to schedule. Explicitly instruct the patient not to take the double of the dose the following day to prevent the patient from attempting to make up the skipped dose.

- If more than 24 hours have elapsed since last dose, study PI should contact the sponsor/Medical Monitor.
If the patient is unable to tolerate the study medication due to intolerable adverse events, they should be withdrawn from the study and appropriate (end of study) procedures should be followed as shown in Table 1.

### 6.2 Formulation, Packaging and Labeling

Study medication consists of RO4917523 pellets in hard gelatin capsules in strengths of 0.5 mg (Ro 491-7523/F18) and 1.0 mg (Ro 491-7523/F19). The capsules are identical in size (no. 1). A matching placebo capsule (Ro 491-7523/F21) is also available.

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

#### 6.2.1 Packaging and Storage

Daily doses will be packaged as single blister strips containing 2 capsules as shown below in Table 3:

<table>
<thead>
<tr>
<th>Table 3</th>
<th>IMP Packaging Configuration by Treatment Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Arm</td>
<td>Number and Type of Capsules</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo Ro 491-7523/F21 0.5 mg Ro 491-7523/F18 1.0 mg Ro 491-7523/F19</td>
</tr>
<tr>
<td>RO4917523 0.5 mg</td>
<td>2 0 0</td>
</tr>
<tr>
<td>RO4917523 1.5 mg</td>
<td>1 1 1</td>
</tr>
</tbody>
</table>

Medication will be packed in blister packs which contain a one week supply. The drug must not be stored at temperatures exceeding 25°C (77°F).

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

### 6.3 Blinding and Unblinding

The Randomization List will not be available at the study center, to the Sponsor’s monitors, project Statisticians, the CRO, or to the project team at Roche (except as noted in section 9 for the analysis of pharmacokinetic samples). Unblinding should not occur except in the case of emergency situations. Any request from the investigator for information about the treatment administered to study patients for another purpose must be discussed with Roche. Unblinding will be performed by means of the Interactive Voice Response System/Interactive Web Response System (IVRS).
As per regulatory reporting requirement, Roche will unblind the identity of the study medication for all unexpected serious adverse events that are considered by the investigator to be related to study drug as per safety reference document(s), e.g., IB, CDS, SPC. Details of patients who are unblinded during the study will be included in the Clinical Study Report.

Unblinding for independent pharmacological analysis of biological samples, or ongoing safety monitoring by a Drug Safety Monitoring Board [DSMB], will be performed according to the sponsor’s internal procedures to ensure integrity of the data.

All other individuals directly involved in this study will remain blinded until the final analysis of the primary parameter.

The password-protected and/or encrypted electronic Master Randomization List is kept by the IVRS vendor in their secure system and is only accessible to the Randomization List Managers. No open key to the code will be available at the study center, to the Sponsor’s monitors, project statisticians, or to the project team at Roche or the CRO.

### 6.4 Accountability of IMP and Assessment of Compliance

#### 6.4.1 Accountability of IMP

The investigator is responsible for the control of drugs under investigation. Adequate records for the receipt (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the study drug must be maintained. Accountability will be assessed by maintaining adequate drug dispensing and return records.

Accurate records must be kept for each study drug provided by the sponsor. These records must contain the following:

- Documentation of drug shipments received from the sponsor (date received and quantity)
- Disposition of unused study drug not dispensed to patient

A Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the patient to whom the study medication was dispensed
- the date[s], quantity of the study medication dispensed to the patient
- the date[s] and quantity of the study medication returned by the patient

All records and drug supplies must be available for inspection by the Monitor at every monitoring visit.

Patients will be asked to return all used and unused drug supply containers at the end of the treatment as a measure of compliance.
When the study is terminated, the investigator will return any used and unused study drug (i.e. empty, partially used, and unused containers) to the Monitor. The completed Drug Dispensing Log and Drug Return Record(s) will be returned to Roche, unless alternate destruction has been authorized by Roche, or required by local or institutional regulations. (Section 6.5). The investigator’s copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to Roche.

6.4.2 Assessment of Compliance

The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records. Patients will be asked to return all used and unused drug supply containers at each study visit as a measure of compliance.

A Drug Dispensing Log must be kept current and should contain the following information:

• the identification of the patient to whom the study medication was dispensed
• the date[s], quantity of the study medication dispensed to the patient
• the date[s] and quantity of the study medication returned by the patient

This inventory must be available for inspection by the monitor. All supplies, including partially used or empty containers and the dispensing logs, must be returned to the monitor at the end of the study.

6.5 Destruction of the IMP/Comparator

Local or institutional regulations may require immediate destruction of used investigational medicinal product (IMP) for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed IMP before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the sponsor at study start up before destruction.

If there are any issues with the drug it should be returned to the appropriate Roche clinical trial supplies department for long-term storage and not destroyed.

Written documentation of destruction must contain the following:

– Identity [batch numbers or subject numbers] of IMP[s] destroyed
– Quantity of IMP[s] destroyed
– Date of destruction
– Method of destruction
7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events (AEs) and Laboratory Abnormalities

7.1.1 Clinical AEs

According to the International Conference of Harmonization [ICH], an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily 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 [investigational] product, whether or not considered related to the medicinal [investigational] product. Pre-existing conditions which worsen during a study are to be reported as AEs.

7.1.1.1 Intensity

All clinical AEs encountered during the clinical study will be reported on the AE form of the CRF. Intensity of AEs will be graded on a three-point scale [mild, moderate, or severe] and reported in detail on the CRF.

<table>
<thead>
<tr>
<th>Mild</th>
<th>discomfort noticed but no disruption of normal daily activity.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>discomfort sufficient to reduce or affect daily activity.</td>
</tr>
<tr>
<td>Severe</td>
<td>inability to work or perform normal daily activity</td>
</tr>
</tbody>
</table>

7.1.1.2 Drug - Adverse event relationship

Relationship of the AE to the treatment should always be assessed by the investigator.

7.1.1.3 Serious Adverse Events [Immediately Reportable to Roche]

A Serious Adverse Event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfils at least one of the following criteria:

- is fatal; [results in death**; NOTE: death is an outcome, not an event]
- is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe]
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
is medically significant or requires intervention to prevent one or other of the outcomes listed above.

**The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably.**

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

### 7.1.2 Treatment and Follow-up of AEs

AEs, especially those for which the relationship to study medication(s) is not “unrelated”, should be followed up until they have returned to baseline status or stabilized. If after follow-up, return to baseline status or stabilization cannot be established an explanation should be recorded on the CRF.

### 7.1.3 Laboratory Test Abnormalities

Laboratory test results will be provided to the sites as faxed reports from the central laboratory vendor.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event [SAE] should be reported as such, in addition to being recorded as an AE in the CRF.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE form in the CRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication [e.g. dose modification, interruption or permanent discontinuation]
- Requiring a change in concomitant therapy [e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment].

**This applies to** any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication, which falls outside the laboratory reference range and meets the clinical significance criteria.

**This does not apply to** any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the clinical significance criteria [these will be analyzed and reported as laboratory abnormalities]; those which are considered AEs of the type explicitly exempted by the protocol; or those which are a result of an AE which has already been reported.

#### 7.1.3.1 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the CRF.
7.2 Handling of Safety Parameters

7.2.1 Reporting of AEs

Adverse events will be recorded from randomization until 21 days following treatment discontinuation. As with all assessments, eCRF completion begins when the patient is randomized in the study. For screen failure patients, the adverse events will only be recorded in source documents.

7.2.1.1 Recording of AEs related to Patient-Reported Outcomes

AE reports will not be derived from PRO data. If during site review of the completed PRO questionnaires a possible AE is identified, site staff will alert the investigator to determine if the criteria for an AE has been met (as described in section 7.1).

7.2.2 Reporting of Serious Adverse Events [immediately reportable]

Any clinical AE or abnormal laboratory test value that is serious [as defined in Section 7.1.1.3 above] and which occurs during the course of the study, regardless of the treatment arm, occurring from the enrollment visit (start of study screening procedures), must be reported to Roche within one working day of the investigator becoming aware of the event [expedited reporting]. The investigator must complete the SAE Reporting Form [gcp_for000031] and forward it to the SAE Responsible.

Additionally, after the informed consent has been signed, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures or medication washout). After first study medication, all SAEs must be reported.

Related Serious Adverse Events MUST be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to investigators at each site and associated IRB/IEC when the following conditions occur:

• The event must be a SAE.
• There must be a certain degree of probability that the event is an adverse reaction from the administered drug.
• The adverse reaction must be unexpected, that is to say, not foreseen in the SPC text (Summary of Product Characteristics (for an authorized medicinal product) or the Investigator’s Brochure (for an unauthorized medicinal product).

When all patients at a particular site are off treatment as defined by the protocol:

• only individual SUSAR reports originating in that particular trial will be forwarded to the site and associated IRB/IEC on an expedited basis;
• individual SUSARs considered to be a significant safety issue and/or which result in Roche recommending a change to the Informed Consent Form (ICF), will be reported in an expedited manner to all investigators and IRBs/IECs;
• SUSAR reports originating from other trials using the same IMP will be provided as six monthly SUSAR Reports (SSRs) to investigators and IRBs/IECs where long-term follow-up studies are carried out, unless they are considered significant.
Unrelated Serious Adverse Events must be collected and reported during the study and for up to 21 days after the last dose of study medication.

This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2. Complete information can be found in Appendix 2.

7.2.3 Abuse and Withdrawal Symptoms

An abuse potential monitoring strategy will ensure close monitoring for potential diversion and/or abuse of study drug as well as adverse events which may be consistent with abuse or withdrawal. The strategy is as follows:

- The PI/site staff will regularly check for patterns of suspected hoarding of study medication (e.g., based on recurring instances of missing medication). Such patterns should be brought to the attention of the Medical Monitor for appropriate follow up.
- The Sponsor/Medical monitor and PI will regularly review all AEs related to abuse potential

Any findings will be documented in a note to file.

7.2.4 Pregnancy

A female patient must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study.

The investigator should report all pregnancies within 24 hours to the sponsor. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. The outcome of the pregnancy must be reported to the sponsor with a follow-up report. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator.

7.3 Warnings and Precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the Investigators Brochure.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Endpoints

8.1.1 Primary Endpoints

Change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

8.1.2 Secondary Endpoints

The secondary endpoints are:

- Change in Clinical Global Scores Severity (CGI-S) from baseline to end of treatment and Improvement (CGI-I) at end of treatment
• Frequency of patients exhibiting remission (a MADRS score of less than or equal to 10) at end of treatment
• Frequency of patients exhibiting response (reduction in MADRS score equal to or greater than 50% of the baseline score) at end of treatment
• Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16) change from baseline to end of treatment
• Patient Global Impression of Improvement (PGI-I) score at end of treatment

8.1.3 Exploratory Endpoints

The key exploratory endpoint is:
• Change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment for exploratory evaluation.

The other exploratory endpoints are:
• The proportion of patients who meet MADRS responder criteria plus CGI-I score of 1) “very much improved” or 2) “much improved” at end of treatment
• The proportion of patients who meet MADRS remission criteria plus CGI-I score of 1) “very much improved” or 2) “much improved” at end of treatment
• The speed of onset of antidepressant effect based on change over time in any of the depression symptom scales
• CANTAB Cognitive Test Battery subset
• Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)
• Sheehan Disability Scale (SDS)

8.1.4 Safety

Safety and tolerability of the treatment will be evaluated by AEs, laboratory tests, vital signs, electrocardiogram, the C-SSRS, BPRS, and YMRS (if appropriate).

All patients who belong to the safety population will be included in the safety evaluation.

8.2 Statistical and Analytical Methods

8.2.1 Analysis Population

8.2.1.1 Intent-to-treat Population

The intent-to-treat (ITT) population will include all patients who were randomized and had a baseline and at least one post-baseline assessment of MADRS (i.e., valid total score). The ITT analysis will be done by randomized treatment. The ITT population will be the primary population for all analyses of primary and secondary clinical efficacy variables.

8.2.1.2 Per-protocol Population

The per-protocol (PP) population will be defined as the subset of the intent-to-treat population. Definition of the PP population will be finalized before the database closure and will be documented in the analysis plan. The definition may include sufficient
treatment duration of study medication, and lack of any major protocol violations that affect efficacy evaluation.

For the PP population analysis, data will be analyzed according to the treatment actually taken.

8.2.1.3 Safety Population

The safety population will consist of all patients who have received at least one dose of study medication, whether withdrawn prematurely or not. All safety data will be analyzed for the safety population according to the medication actually dispensed.

8.2.2 Statistical Model

All efficacy data will be analyzed using intent-to-treat population. PP analysis will be conducted for the primary and selected secondary efficacy variables only if more than 10% of the ITT population are not included in the PP population (defined in 8.2.1.2). For all efficacy variables, the baseline value will be defined as the last value taken prior to the start of double-blind study medication.

The efficacy parameters of the primary endpoint and of the continuous secondary endpoints will be analyzed using a mixed effects covariance pattern model to utilize all the data collected over time with consideration of the variance-covariance matrix of the repeated measures (MMRM).

The model will include independent variables of the fixed, categorical effects of treatment, geographical region/countries, assessment weeks relative to the first dose of study medication (i.e., time), and treatment-by-time interaction, along with the continuous effect of baseline. The geographical region/countries will use as categories the strata of the randomization: Europe, United States, Latin America, Asia (excluding Japan) and Japan.

An unstructured variance-covariance matrix will be applied to model the within-patient errors. A treatment-by-time interaction contrast will be used to estimate the difference between each of the RO4917523 doses and placebo in the mean change from baseline to day 42 of randomized treatment.

As additional sensitivity analysis, the primary efficacy variable will also be assessed at day 42 by ANCOVA using the LOCF method as exploratory analysis to assess the robustness of the results. The model will include the baseline measure as covariate, and the categorical variable treatment. The effect size of each dose compared to placebo and its 90% confidence interval will be calculated using estimates from the treatment contrasts. The results will be used for internal decisions on the continuation of the development of the project.

Ordered categorical data, like CGI-S, CGI-I or PGI-I, will be analyzed using Wilcoxon rank test. Binary data, such as responders or remissions, will be analyzed using Fisher’s exact test.

All exploratory variables and safety and tolerability will be summarized descriptively.
8.2.3 Sample Size

A sample size of approximately 100 patients per group (approximately 300 for 3 groups) has been chosen to obtain a power of approximately 80% at two-sided maximum familywise error rate of 0.05 in a closed testing procedure.

The power calculation was based on simulations of the MMRM analysis planned for the primary efficacy variable. The following assumptions were included:

- 7 post-baseline assessment visits
- Overall dropout rate of 15%, incremental rates over the 6 week period
- An effect size of 0.46 for one dose group at day 42 assuming increasing magnitude of treatment difference over the period and an effect size of 0.0 for the other dose group
- A moderately decreasing correlation structure between assessments that are further apart

8.2.4 Hypothesis Testing

For the primary endpoint the following hypotheses will be tested:

$$H_0: \text{The mean reduction in total MADRS score at end of treatment in both dose groups are same as in the Placebo group} \quad \mu_{RO\,1} = \mu_{Placebo} = \mu_{RO\,2}$$

vs.

$$H_1: \text{At least in one dose group the mean reduction in total MADRS score at end of treatment is different from the Placebo group} \quad \mu_{RO\,1} \neq \mu_{Placebo}\, or\, \mu_{RO\,2} \neq \mu_{Placebo}$$

For each dose group i=1,2 the following hypotheses will be tested:

$$H_0_i: \text{The mean reduction in total MADRS score at end of treatment in dose group i is the same as in the Placebo group} \quad \mu_{RO\,i} = \mu_{Placebo}$$

vs.

$$H_1_i: \text{The mean reduction in total MADRS score at end of treatment in dose group i is different from the Placebo group} \quad \mu_{RO\,i} \neq \mu_{Placebo}$$

A closed testing procedure will be utilized: The overall hypothesis $H_0$ will be tested at the two-sided significance level $\alpha = 0.05$ using the Dunnett’s test within the MMRM analysis. If $H_0$ will be rejected, the elementary hypothesis $H_0_i$ will be tested at the two-sided significance level $\alpha = 0.05$ utilizing t-test within MMRM, separately for i=1, 2. The closed testing procedure has a two-sided maximum family-wise error rates of 0.05. Therefore no further adjustment for multiplicity is required.

8.2.5 Efficacy Analysis

8.2.5.1 Interim Analysis

No interim analyses are planned.
8.2.5.2  **Missing Data Handling**

The main analysis of the primary and continuous secondary efficacy variables will be done using a mixed effects model, and no imputation for missing data will be applied.

To understand the pattern of missing data observed during the study and thus the missing data mechanism, the following data will be reviewed:

- Timing of discontinuations by treatment group
- Reasons for discontinuation by treatment group and time
- Mean of the primary efficacy variable of those who dropped out vs. those who remained at each scheduled assessment week

A sensitivity analysis for deviation from the assumption for the randomness of missing data as required for the MMRM analysis (Missing at Random) will be performed. Details will be described in the statistical analysis plan prior to database lock and unblinding.

8.2.6  **Safety Data Analysis**

All safety variables (e.g., adverse events, lab tests, ECG, vital signs, BPRS, YMRS) will be summarized for each assessment time (including follow-up) using descriptive statistics. The items of the C-SSRS will be presented by individual listings and the outcomes from this scale will be classified using the C-CASA methodology. Incidence of AEs will be summarized based on body systems and preferred terms. Incidence of marked abnormal lab test results will be summarized based on the Roche COG 3007 definition.

8.2.7  **Other Analyses**

8.2.7.1  **Pharmacokinetic Analysis**

Nonlinear mixed effects modeling (with software NONMEM [20]) will be used to analyze the sparse sampling dose-concentration-time data of RO4917523. Population and individual pharmacokinetic parameters (e.g. Cl/F and Vss/F) will be estimated and the influence of various covariates on these parameters will be investigated. The data collected in this study may be pooled with data collected in previous phase I and phase IIa studies as appropriate to build pharmacokinetic model. Secondary PK parameters such as AUC and Cmax will be derived from the individual post-hoc predictions.

The results will be reported in a document separate from the clinical study report.

8.2.7.2  **Pharmacodynamic Analysis**

Exploratory analyses or modeling techniques (if possible) will be used to investigate the relationship between RO4917523 exposure and response (e.g. MADRS, CGI-I for efficacy and occurrence of psychiatric AEs for safety). The results will be reported in a document separate from the clinical study report.

8.2.7.3  **Subgroup Analysis**

To assess whether safety, efficacy and pharmacokinetic results of the patients enrolled in different geographical regions/countries are similar, selected key data may be analyzed for each. The comparability will be assessed descriptively.
9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Contract Research Organization (CRO) Standard Operational Procedures.

Data for this study will be recorded via an Electronic Data Capture system EDC using electronic Case Report Forms (eCRF). It will be transcribed by the site from the paper source documents into the eCRF. In no case is the eCRF to be considered as source data for this trial.

Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the investigator’s records by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the investigator.

A comprehensive validation check program will verify the data. Discrepancies will be generated automatically in the system at the point of entry or added manually for resolution by the Investigator.

In order to facilitate analysis of the pharmacokinetic samples collected in this study, the treatment code will be released to the responsible analyst when the samples have been received at the analytical site and are ready for assay. The result of the analysis must not be released with individual identification of the patient until the database is closed.

9.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

10. STUDY COMMITTEES

An independent Data Safety Monitoring Board (DSMB) will review potential safety signals of concern. The DSMB will be composed of non-sponsor members who are not involved in the conduct of this study and with no other ongoing financial relationship with the sponsor. The DSMB will review available safety data (and potentially efficacy data, only if deemed necessary to better assess safety) from this trial at regularly scheduled intervals as specified in the DSMB Charter. Two DSMB review cycles are planned. The first review cycle is planned to occur when approximately 40 to 60 patients have completed the study. The second will occur when approximately 140 to 160 patients have completed. The DSMB has the option to change the data review schedule as deemed necessary.

Following each data review, the DSMB will make recommendations regarding the conduct of this study, including continuing the study without modifications, or to modify the study design in any other way. Details of the DSMB’s responsibilities and logistics will be outlined in the DSMB Charter.
11. REFERENCES


PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the “Declaration of Helsinki” or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in “Guideline for Good Clinical Practice” ICH Tripartite Guideline or with local law if it affords greater protection to the subject. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the USA or under US IND, the investigator will additionally ensure adherence to the basic principles of “Good Clinical Practice” as outlined in the current version of 21 CFR, subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Subjects”, and part 56, “Institutional Review Boards”.

In other countries where a “Guideline for Good Clinical Practice” exists, Roche and the investigators will strictly ensure adherence to the stated provisions.

12.2 Informed Consent

Written Informed Consent from Patients:

12.2.1 Main study Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator [if acceptable by local regulations], to obtain signed informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The Case Report Forms (CRFs) for this study contain a section for documenting patient informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

12.2.2 RCR Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable under local regulations), to obtain written informed consent from each individual who has consented to RCR sampling after adequate explanation of the aims, methods, objectives and potential hazards. Patients must receive an explanation that they are completely free to refuse to provide the RCR specimen(s) and may withdraw his/her sample at any time and for any reason during the 15 year storage period of the specimen(s). The Informed Consent for an optional specimen donation will be
incorporated as a specific section into the main Clinical Trial [or Experimental Research study] Informed Consent Form (ICF). A second, separate, specific signature consenting to specimen donation will be required to document the study participant’s agreement to provide an optional specimen; if the participant declines, he/ she will check a “no” box in the appropriate section and not provide a second signature.

The CRF for the associated clinical study contains a page for documenting patient informed consent to the RCR, and this must be completed appropriately.

12.2.3 Death or Loss of Competence of Participant who has donated a specimen(s) that is stored in the RCR

In case the Informed Consent Form and/or the Study Protocol do not provide any specific provisions for death or loss of competence, specimen and data will continue to be used as part of RCR research.

In the event of the death of a participant of a Roche Clinical Trial or Experimental Medicine Research study or if a participant is legally incompetent at the time of the specimen and data procurement, or becomes legally incompetent thereafter, applicable provisions as stated for such situations in the respective Informed Consent Form and/or the Study Protocol shall become effective and be followed accordingly.

Additional procurement of assent from legally incompetent persons and minors shall take place according to local laws and international best practice, as it applies to the specific case.

12.3 Independent Ethics Committees/(IEC)Institutional Review Board(IRB)

The protocol, informed consent and any accompanying material provided to the patient in the U.S. will be submitted by the investigator to an IRB for review. For EEA member states, the sponsor will submit to the Competent Authority and IEC, the protocol and any accompanying material provided to the patient. In both the US and EEA member states, the accompanying material may include patient information sheets, descriptions of the study used to obtain informed consent and terms of any compensation given to the patient as well as advertisements for the trial.

An approval letter or certificate (specifying the protocol number and title) from the IEC/IRB must be obtained before study initiation by the investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.

Any modifications made to the protocol, informed consent or material provided to the patient after receipt of the IEC/IRB approval must also be submitted by the investigator in the U.S. and by the Sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the investigator in submitting the protocol to the European Ethics Review Committee.
Sampling for the RCR is contingent on review and approval for the exploratory biomarker assessments and written informed consent by an appropriate regulatory body (depending on the country where the study is performed) and a site’s Institutional Review Board (IRB) / Ethics Committee (EC). If a regulatory or site’s IRB/EC does not approve the sampling for the exploratory assessments the section on biomarker sampling will not be applicable.

Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study. In the U.S. Roche submits an IND Annual Report to the FDA according to local regulatory requirements and timelines.

12.4 **Role of the Science and Ethics Advisory Group (SEAG)**

A Science and Ethics Advisory Group consisting of experts in the fields of biology, ethics, sociology and law will advise Roche regarding the use of specimens stored in the RCR and on the scientific and ethical aspects of handling genetic information. The SEAG is independent of Roche.

13. **Conditions for Modifying the Protocol**

Requests from investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the sponsor and the investigator [investigator representative[s] in the case of a multicenter trial]. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Clinical Science Leader and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change[s] involves only logistical or administrative aspects of the trial [e.g. change in monitor[s], change of telephone number[s]].

14. **Conditions for Terminating the Study**

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the investigator will assure that adequate consideration is given to the protection of the patients’ interests. The appropriate IRB/EC and Regulatory Agencies should be informed accordingly.

15. **Study Documentation, CRFs and Record Keeping**

15.1 **Investigator's Files / Retention of Documents**

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories [1] Investigator's Study File, and [2] patient clinical source documents.
The Investigator's Study File will contain the protocol/amendments, CRF/DCS and
schedule of assessments, Independent Ethics Committee/Institutional Review Board and
governmental approval with correspondence, sample informed consent, drug records,
staff curriculum vitae and authorization forms and other appropriate
documents/correspondence, etc. In addition at the end of the study the investigator will
receive the patient data, which includes an audit trail containing a complete record of all
changes to data, query resolution correspondence and reasons for changes, in human
readable format on CD which also has to be kept with the Investigator’s Study File.

Patient clinical source documents [usually defined by the project in advance to record key
efficacy/safety parameters independent of the CRFs] would include patient hospital/clinic
records, physician's and nurse's notes, appointment book, original laboratory reports,
ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent
forms, consultant letters, and patient screening and enrollment logs. The Investigator
must keep the two categories of documents as described above (including the archival
CD) on file for at least 15 years after completion or discontinuation of the study. After
that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to
another location, Roche must be notified in advance.

If the Investigator can not guarantee this archiving requirement at the investigational site
for any or all of the documents, special arrangements must be made between the
Investigator and Roche to store these in a sealed container[s] outside of the site so that
they can be returned sealed to the Investigator in case of a regulatory audit. Where source
documents are required for the continued care of the patient, appropriate copies should be
made for storing outside of the site.

ICH GCP guidelines require that Investigators maintain information in the study patient’s
records which corroborate data collected on the CRF(s). Completed CRF will be
forwarded to Roche.

### 15.2 Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data
from the study documentation or clinic records. This is particularly important when errors
in data transcription are suspected. In case of special problems and/or governmental
queries or requests for audit inspections, it is also necessary to have access to the
complete study records, provided that patient confidentiality is protected.

### 15.3 Audits and Inspections

The investigator should understand that source documents for this trial should be made
available to appropriately qualified personnel from the Roche Pharma Development
Quality Assurance Unit or its designees, or to health authority inspectors after appropriate
notification. The verification of the CRF data must be by direct inspection of source
documents.
15.4 Case Report Forms or Electronic Case Report Forms

Data for this study will be captured via an online Electronic Data Capture (EDC) system. The data collected in the source documents is entered onto the study eCRF. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change.

For each patient randomized, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

15.5 Financial Disclosure

The investigator(s) will provide the Sponsor with sufficient accurate financial information (PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

16. Monitoring the Study

It is understood that the responsible Roche monitor [or designee] will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial [CRFs and other pertinent data] provided that patient confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the patient received the study drug assigned by the randomization center (by controlling the written confirmation of the randomization by IVRS). The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF.

The investigator [or deputy] agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Roche Clinical Repository specimens will at all times be tracked in a manner consistent with Good Clinical Practice, by a quality controlled, auditable and validated Laboratory Information Management System, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in the study protocol and ICF, respectively. Roche monitors and auditors will have direct access to appropriate parts of records relating to patients participating in this study for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, Institutional Review Board/Independent Ethics Committee (IRB/IEC) review, and regulatory inspections by
providing direct access to source data and documents related to the RCR Research Project.

17. **CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS**

The investigator must assure that patients’ anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrollment log showing codes, names and addresses. The investigator should maintain documents not for submission to Roche, e.g., patients' written consent forms, in strict confidence.

Roche already maintains rigorous confidentiality standards for clinical studies by “coding” (i.e. assigning a unique patient ID number at the investigator site) all patients enrolled in Roche clinical studies. This means that patient names are not included in data sets that are transmitted to any Roche location. Given the sensitive nature of genetic data, Roche has implemented a number of additional processes to assure patient confidentiality. All specimens taken for inherited genetic research that will be stored in the RCR (see 5.6.1) undergo a second level of “coding”. At Roche, the specimen is transferred to a new tube and labeled with a new random number. This is referred to as “Double Coding (De-Identification)”. Data generated following the use of these specimens and all clinical data transferred from the clinical study database and considered relevant, will also be labeled with this same code. The “linking key” between the participant’s identification number and this new independent code will be stored in a secure database system. Access to the table linking the participant identification number to the specimen code will be strictly limited and monitored by audit trail. Legitimate operational reasons for accessing the “linking key” will be documented in a standard operating procedure. Access to the “linking key” for any other reason will require written approval from the Governance Committee responsible for the specimen(s).

18. **CLINICAL STUDY REPORT (CSR)**

A clinical study report will be written and distributed to Health Authorities as required by applicable regulatory requirements.

To fulfill the requirement of the EU Directive No 75/318/EEC the CSR will be signed by a coordinating investigator who will be designated at a later stage.

Note: EU Regulation (EC) No.1901/2006, states: For pediatric studies the CSR must be distributed to the applicable Health Authorities within six months of completion of the study.

19. **PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS**

Roche will comply with the requirements for publication of study results.

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

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

Data derived from RCR specimen analysis on individual patients will not be provided to study investigators, except where explicitly stipulated in a study protocol (e.g. if the result is an enrollment criterion). Exceptions may be granted (e.g. if biomarker data would be linked to safety issues). The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements and/or know-how originating from the use of the RCR will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.
Appendix 1  AEs Categories for Determining Relationship to Test Drug

PROBABLE [must have first three]

This category applies to those AEs which are considered, with a high degree of certainty, to be related to the test drug. An AE may be considered probable, if:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It cannot be reasonably explained by the known characteristics of the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It disappears or decreases on cessation or reduction in dose. [There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [1] bone marrow depression, [2] tardive dyskinesias.]
4. It follows a known pattern of response to the suspected medication.
5. It reappears upon rechallenge.

POSSIBLE [must have first two]

This category applies to those AEs in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possible if, or when:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It may have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It follows a known pattern of response to the suspected medication.

REMOTE [must have first two]

In general, this category is applicable to an AE which meets the following criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug.
2. It may readily have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It does not follow a known pattern of response to the suspected medication.
4. It does not reappear or worsen when the drug is readministered.

UNRELATED

This category is applicable to those AEs which are judged to be clearly and incontrovertibly due only to extraneous causes [disease, environment, etc.] and do not meet the criteria for drug relationship listed under remote, possible, or probable.
## Appendix 1  AEs Categories for Determining Relationship to Test Drug

(Cont.)

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<th>Probable</th>
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<td>–</td>
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<td>+</td>
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<td>Reasonable temporal association with drug administration</td>
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<tr>
<td>May be produced by patient clinical state, etc.</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Known response pattern to suspected drug</td>
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<td>Disappears or decreases on cessation or reduction in dose</td>
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<td>–</td>
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<tr>
<td>Reappears on rechallenge</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>
Appendix 2  ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- is fatal; [results in death] [NOTE: death is an outcome, not an event]
- is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe]
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor 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 patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are 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.

An unexpected AE is one in which the nature or severity is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For Serious Adverse Events, possible causes of the event is indicated by selecting one or more options. (Check all that apply)

- Pre-existing/Underlying disease – specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g. accident, new or intercurrent illness) – specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours’ duration may be rated as severe, but may not be clinically serious.
Appendix 2  ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

[Cont.]

A serious adverse event occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test “drug”, should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs form of the CRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor:

See attached Protocol Administrative and Contact Information & List of Investigators Form, [gcp_for000227], for details of administrative and contact information.

ROCHE HEADQUARTERS CONTACT for SAEs and other medical emergencies: Clinical Operations/Clinical Science:

See attached Protocol Administrative and Contact Information & List of Investigators form, [gcp_for000227], for details of administrative and contact information.

24 HOUR MEDICAL COVERAGE:

Identification of a contact for 24 Hour Medical Coverage is mandatory to be compliant with worldwide regulatory agencies and to ensure the safety of study patients.

An Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with the Roche medical contact for this study and track all calls. The Emergency Medical Call Center Help Desk will be manned 24 hours 7 days a week. Toll free numbers will be distributed to all investigators running Roche Pharma Development clinical trials. The Help Desk will be used for medical emergencies outside regular business hours, or when the regular Clinical Science Leader/Clinical Pharmacology Leader cannot be reached.

See the attached Protocol Administrative and Contact Information & List of Investigators form, [gcp_for000227], for details of administrative, contact information, and Emergency Medical Call Center Help Desk toll-free numbers.
Appendix 3  Structured Interview Guide For The Montgomery And Asberg Depression Rating Scale (Madrs-Sigma)

Source [12]

INTERVIEWER: The questions in bold for each item should be asked exactly as written. Often these questions will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. Note that questions in parentheses are optional, for use, for example, if information is unknown.

NOTES:

Time period. The ratings should be based on the patient's condition in the past week.

Change from baseline. In general, a symptom is rated as present only when it reflects a change from before the depression began (baseline). The interviewer must identify a 2-month period of non-depressed functioning and use this as a reference point. In some cases, such as when the patient has dysthymia the referent should be to the last time the person felt all right (i.e. not depressed or high) for at least a few weeks.

This interview guide is based on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry ;1979 134: 382-9). The scale itself has been retained in its original form, except for reversing the order of the first two items. This guide adds interview questions to aid in the assessment and application of the MADRS. Previous versions of this guide appeared in 1988, 1992, 1996, and 2005.

©2008 The Royal College of Psychiatrists. The SIGMA may be copied by individual researchers or clinicians for their own use without seeking permission from the publishers. The scale must be copied in full and all copies must acknowledge the following source: Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). Br J Psychiatry 2008; 192: 52-58. Written permission must be obtained from the Royal College of Psychiatrists for copying and distribution to others or for replication (in print, online or by any other medium). Correspondence should be addressed to Dr. J Williams, MedAvante, Inc., 100 American Metro Blvd., Suite 106, Hamilton, NJ 08619, USA; email: jbw5@columbia.edu To inform an ongoing survey, researchers and clinicians are asked to notify Dr Williams of their intention to use the SIGMA.

*NOTE: Scale removed due to copyright protection.*
Appendix 4  Clinical Global Impression (CGI)

Source [13]

Clinical Global Impression – Severity of Illness (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

1 = normal, not at all ill
2 = borderline mentally ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill patients

Clinical Global Impression – Improvement (CGI-I)

Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his/her condition at admission to the study, how much has he/she changed?

1 = very much improved
2 = much improved
3 = minimally improved
4 = no change
5 = minimally worse
6 = much worse
7 = very much worse

Appendix 5  Patient Global Impression of Improvement (PGI-I)

Check the one number that best describes how your depression is now, compared with how it was before you began taking medication in this study.

1 = very much better
2 = much better
3 = a little better
4 = no change
5 = a little worse
6 = much worse
7 = very much worse
Appendix 6  Quick Inventory of Depressive Symptomatology Self Report (16-Item) (Self-Report) (QIDS-SR16)

Source [14, 15]

*NOTE: Scale removed due to copyright protection. Please see www.ids-qids.org/ for more information.*
Appendix 7  Quality of Life Enjoyment and Satisfaction Questionnaire- Short Form (Q-LES-Q-SF)

Source [16]

QUALITY OF LIFE ENJOYMENT AND SATISFACTION QUESTIONNAIRE – SHORT FORM*

(Q-LES-Q-SF)

Jean Endicott, Ph.D**

This questionnaire is designed to help assess the degree of enjoyment and satisfaction experienced during the past week.

Name ______________________ ID# ___ ___ ___ ___ ___ ___ ___ ___ Date: ___ / ___ / ___

(3-10)+ (11-16)+

Sex: 1 - Male, 2 - Female Age: ___ ___

(17)+ (18-19)+

Study # ___ ___ 3687 Group: ___ ___ ___

(20-21)+ (22-24)+ (79-80 = DA+)

* The Short Form of the Q-LES-Q has the same content as the general activities section of the regular Q-LES-Q.

** Developed with the assistance of Wilma Harrison, M.D. and Dianne Schechter, Ph.D. (11/29/90)

Available from Jean Endicott, Ph.D., Department of Research Assessment and Training, Unit 123, 1051 Riverside Drive, New York, NY 10032. (Under Copyright)

NOTE: Scale removed due to copyright protection.
Appendix 8 Sheehan Disability Scale (SDS)

Source [17]

*NOTE: Scale removed due to copyright protection.*
Appendix 9  Brief Psychiatric Rating Scale, Positive Symptom Subscale
(4 items)

Source [18]

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Please enter the score for the term which best describes the patient’s condition

0 = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe

Item 4. Conceptual Disorganization

Degree to which the thought processes are confused, disconnected, or disorganized, Rate on the basis of integration of the verbal products of the patient.

Do not rate on the basis of patient’s subjective impression of his own level of functioning.

Score □

Item 11. Suspiciousness

Belief (delusional or otherwise) that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.

Score □

Item 12. Hallucinatory Behavior

Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.

Score □

Item 15. Unusual Thought Content

Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.

Score □

Adapted from Overall JE, Gorham DR: „The Brief Psychiatric Rating Scale. „Psychological Reports 10:799-812. 1962
Appendix 10   Young Mania Rating Scale (YMRS) (item 1)
Source [19]

*NOTE: Scale removed due to copyright protection.

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STATISTICAL ANALYSIS PLAN

TITLE: A randomized, double-blind, parallel-group study of the safety and efficacy of RO4917523 versus placebo, as adjunctive therapy in patients with major depressive disorder with inadequate response to ongoing antidepressant treatment.

PROTOCOL NUMBER: NP25620
IND NUMBER: 103001
EUDRACT NUMBER: 2011-001436-33
SPONSOR: F. Hoffmann-La Roche Ltd

SAP APPROVAL

Plan Number / Version: 1
Date: See last date in electronic signature manifestation below.
Plan approved by: See electronic signature manifestation below.

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1. BACKGROUND

This Statistical Analysis Plan (SAP) documents the statistical methods for summarizing and analyzing the efficacy and safety data from study NP25620 to be collected from patients with major depressive disorder with an inadequate response to ongoing antidepressant treatment who will be administered RO4917523. The main purpose of this SAP is to describe the data handling rules, derivation rules, and statistical analysis methods.

2. STUDY DESIGN

Study NP25620 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study that will evaluate two fixed doses of RO4917523 versus placebo as adjunctive treatment for 6 weeks in patients with major depressive disorder with inadequate response to ongoing antidepressant therapy.

Following screening procedures to confirm eligibility, patients on ongoing antidepressant therapy will be randomized to one of the three treatment arms: a) RO4917523 0.5 mg once daily, b) RO4917523 1.5 mg once daily, or c) placebo once daily.

This outpatient trial consists of the following periods:

- Screening period: up to 14 days
- Double-blind treatment period: 6 weeks
- Follow-up period: 21 days

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1.

2.2 OUTCOME MEASURES

See the protocol synopsis in Appendix 1 for the efficacy, safety, and pharmacokinetic (PK) outcome measures.

2.3 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 100 patients per group (approximately 300 patients for the three groups) has been chosen to obtain a power of approximately 80% at two-sided maximum family-wise error rate of 0.05 in a closed testing procedure. The power calculation was based on simulations of the mixed-effect model repeat measures (MMRM) analysis planned for the primary efficacy variable. The following assumptions were included:

- Seven post-baseline assessment visits
- An overall dropout rate of 15%, incremental rates over the 6-week double-blind treatment period
• An effect size of 0.46 for one dose group at Day 42, assuming increasing magnitude of treatment difference over the period and an effect size of 0.0 for the other dose group.

• A moderately decreasing correlation structure between assessments that are further apart.

2.4 ANALYSIS TIMING
The primary efficacy analysis will be performed at the end of the study, after the last patient has completed the last follow-up visit.

2.4.1 Data to Be Analyzed
In the case that (safety) follow-up data and patient data from the additional Japanese patients will continue after the primary and secondary efficacy analysis, the efficacy analysis will be carried out by an independent group consisting of the Sponsor and the contract research organization as described in Section 2.4.2. In this case, the unblinded Sponsor’s Neuroscience Therapeutic Area Head and/or designees will have no contact with the study management team regarding the conduct of the study and data cleaning activities until final database lock.

2.4.2 Measures to Minimize Bias
The randomization list will only be provided to the independent group. The data will be stored in an access-restricted area to which only the independent group will have access. Unblinded summary data will be reviewed only by the Neuroscience Therapeutic Area Head and/or designees who will have no contact with the study management team regarding the conduct of the study and data cleaning activities until database lock. The results will be presented to representatives from upper management who will be involved directly in the decision on the planning of future research for this project. Dissemination of the results will be limited, and, particularly, the details will not be distributed to those who are directly involved the conduct of the study, and the data cleaning activities.

An audit trail will be maintained to track any changes made to efficacy data points between the efficacy analysis and final database lock. If any change in the variables used for the analysis occurs, the respective analyses will be repeated and both results will be reported in the CSR.

3. STUDY CONDUCT
3.1 RANDOMIZATION
Randomization will be performed centrally by telephone or web using an interactive response system (IxRS). After being screened, those patients who meet all eligibility criteria will be randomly assigned to one of the three treatment groups: placebo, RO4917523 0.5 mg, or RO4917523 1.5 mg, in the ratio of 1:1:1.
The patient numbers will be allocated sequentially in the order in which the patients are enrolled according to the specification document agreed with the IxRS vendor. The treatment allocation will be stratified by geographical region/country, as follows:

- Europe, United States, Latin America, and Japan

The study is planned in a double-blind manner to minimize potential bias. The Sponsor will be blinded to the study treatments (those patients are randomized to and those actually given).

3.2 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will review unblinded safety data at scheduled time intervals and on an ad-hoc basis as needed. The safety data package will be prepared by a team external to the Sponsor. Details are described in the iDMC Charter.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

The following analysis populations will be defined: intent to treat (ITT), per-protocol (PP), completer (CP) and safety.

4.1.1 Intent-to-Treat Analysis Population

The ITT analysis population will include all randomized patients who received at least one dose of the randomized study drug. Patients who receive study drug different from that to which they were randomized will be included in the group to which they were randomized.

The ITT analysis population will be the primary analysis population for all analyses of primary and secondary clinical efficacy data.

4.1.2 Per Protocol Population

The PP analysis population will be defined as the subset of the ITT population that excludes those patients who have major protocol violations affecting efficacy assessments. Patients in the PP population should meet all the following criteria:

- Meet all inclusion criteria with the exception of the body mass index (BMI) requirement, contraceptive protections, and stability of existing medication regimens for other medical conditions for at least 6 weeks prior to baseline
- Show overall compliance of 80%–120% with study drug during the individual treatment period (Day 42/end of treatment [EOT]) (see Section 4.7.1 for calculation of compliance)
- Have assessment of Montgomery Asberg Depression Rating Scale (MADRS) conducted by certified site raters
• Have valid primary efficacy variable values (rater MADRS total score) at baseline and at least one post-baseline treatment assessment

• Have none of the following protocol violation codes: pregnancy positive, ongoing antidepressant medication modified or non-SSRI/SNRI, prohibited medication

If, during the active phase of treatment the patients receive a drug other than the one to which they were randomized and if overall compliance is within 80%−120%, the efficacy variables will be analyzed for this population on the basis of the actual treatment received.

PP analyses will be performed on the primary efficacy endpoint if a >10% difference exists between the ITT and PP populations in the number of patients qualified to be assessed for consistency of the results between the two populations.

### 4.1.3 Completer Analysis Population

The CP analysis population will be defined as the subset of the PP population that excludes those patients with an incomplete treatment period. Patients in the CP population should meet all the following criteria:

- Completed 6 weeks of double blind treatment (i.e. duration of treatment ≥40 days)
- Have valid primary efficacy variable values (MADRS total score) at baseline and Day 42

If, during the active phase of treatment the patients receive a drug other than the one to which they were randomized and if overall compliance is within 80%−120%, the efficacy variables will be analyzed for this population on the basis of the actual treatment received.

CP analyses will be performed on the primary efficacy endpoint if a >10% difference exists between the CP and ITT populations in the number of patients qualified to be assessed for consistency of the results between the two populations.

### 4.1.4 Safety Analysis Population

The safety analysis population will consist of all patients who have received at least one dose of randomized study medication, regardless of whether they withdrew prematurely or not. Patients whose first randomized study medication received differed from the medication to which they were randomized will be included in the group according to the first randomized study medication actually taken.

All safety parameters will be summarized and presented in tables based on this safety population.
4.2 ANALYSIS OF STUDY CONDUCT

4.2.1 Study Enrollment

- The number of patients for each of the ITT, PP, and safety populations will be summarized by treatment group.
  - The number of patients excluded from each of the populations will be summarized by reason for exclusion.
- The number of patients enrolled at each site will be summarized by treatment group.

4.2.2 Protocol Violations

The major protocol violations will be identified according to the Management of Violations to Protocol Specifications document and recorded on the Roche PD 99V Form before database lock. The number and percentage of patients with major protocol violations will be summarized by treatment group and protocol violation criterion.

4.2.3 Patient Disposition

The number and percentage of patients in each treatment group will be summarized by duration (based on the last dosing day and the date of last contact day, respectively) and reason for withdrawal during the treatment period and follow-up period, respectively.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Summary tables of demographics and baseline disease characteristics will be produced for the ITT and safety populations. No formal hypothesis tests will be performed.

4.3.1 Demographics

Summary statistics will be presented for each treatment group for the following demographics and baseline characteristics: sex, age, race, ethnicity, geographic region/country (Europe, United States, Latin America, and Japan), female reproductive status, weight, height, BMI, smoking status/history, and years of education.

4.3.2 Baseline Disease Characteristics

Summary statistics will be presented for each treatment group for the following baseline disease characteristics: MADRS total rater score, Clinical Global Impression of Severity (CGI-S), and others if appropriate.

4.3.3 History of Major Depressive Disorder

Summary statistics and listings will be generated for each treatment group for patient’s history of major depressive disorder. The key variables from the electronic Case Report Form (eCRF) pages for the psychiatric history and evaluation of depression will be summarized.
4.3.4 Other Diseases Previous and Current at Baseline

For all diseases (other than depression), the term entered by the investigator to describe the disease (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) and system organ class based on the Medical Dictionary for Regulatory Activities (MedDRA). All analyses will be performed using these preferred terms and body systems. Diagnoses will be categorized as “not active,” or “active” at the screening visit, using the end date or “ongoing” tick box responses on the Medical History page of the eCRF.

The number and percentage of patients with previous diseases (i.e., those marked “not active”) will be summarized by treatment group. Multiple occurrences of a same disease (i.e., same coded term) in the same patient will be counted only once. Diseases concurrent at baseline (i.e., those marked “active”) will be summarized similarly in a separate table.

4.3.5 Previous and Concomitant Medications (Other than Study Treatment)

For all medications, the term entered by the investigator to describe the medication (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) and drug class based on the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary. All analyses will be performed using these preferred terms and medication classes.

The number and percentage of patients taking each medication will be presented for each treatment group. Previous and concomitant medications will be summarized separately by the purpose of the treatment (e.g., for depression treatment, for adverse events [AEs], etc.). Previous medications completed 6 months prior to screening will not be summarized. Multiple occurrences of a same medication taken by same patient (i.e., same coded term) will be counted only once. All summary tables will be sorted by medication class (in decreasing order of overall incidence), then by preferred term (in decreasing order of overall incidence).

The rules shown in Table 1 will be applied in classifying the medications into previous, concomitant, or previous and concomitant.
### Table 1  Classification of Treatment Period for Medications

<table>
<thead>
<tr>
<th>CRF page where reported</th>
<th>Medication Start Date</th>
<th>Medication End Date</th>
<th>Assigned Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous and concomitant treatments</td>
<td>Missing, or before start date of first dose of study medication</td>
<td>Before start date of first dose of study medication and ongoing box not checked</td>
<td>PREVIOUS</td>
</tr>
<tr>
<td></td>
<td>Missing, or before start date of first dose of study medication</td>
<td>On or after start date of first dose of study medication or ongoing box checked</td>
<td>PREVIOUS_CONCOMITANT</td>
</tr>
<tr>
<td></td>
<td>Before start date of first dose of study medication</td>
<td>Missing and ongoing box not checked</td>
<td>PREVIOUS_CONCOMITANT</td>
</tr>
<tr>
<td></td>
<td>On or after start date of first dose of study medication</td>
<td>Missing</td>
<td>CONCOMITANT</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>Missing</td>
<td>PREVIOUS_CONCOMITANT</td>
</tr>
</tbody>
</table>

### 4.4 EFFICACY ANALYSIS

All efficacy data collected will be grouped by actual assessment visit day relative to the first day (i.e., Day 1) or last day of randomized study drug.

For the screening assessments, the scheduled visit will be used regardless of the actual assessment days relative to the first day of study drug.

In general, the baseline value will be defined as the last non-missing value recorded prior to or on the first day of the study drug, using the latter if both are available.
Other assessments during the double-blind period and follow-up period will have the following time windows:

<table>
<thead>
<tr>
<th>Visit</th>
<th>Start Day</th>
<th>End Day</th>
<th>Target Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Day 7</td>
<td>5</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Day 11</td>
<td>10</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Day 14</td>
<td>13</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Day 21</td>
<td>18</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Day 28</td>
<td>25</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Day 35</td>
<td>32</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>Day 42</td>
<td>39</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Date of last dose + 18</td>
<td>Date of last dose + 24</td>
<td>Date of last dose + 21</td>
</tr>
</tbody>
</table>

Note that the above defined time windows (day intervals) will be used for all parameters, including those that were not scheduled to be collected at all visits for the sake of consistency. Data from assessments performed during a visit unscheduled for the parameter will not be included in summary tables or hypothesis testing.

If multiple valid (non-missing) values for a variable are recorded at the same time window, one record will be selected for summary of the data by the following priority:

1. The originally scheduled visit assessment
2. The assessment closest to the target assessment day
3. The last assessment within the time window

### 4.4.1 Primary Efficacy Endpoint

#### 4.4.1.1 Definition of Primary Efficacy Endpoint

The primary efficacy endpoint of the study is the change from baseline in the MADRS total score at Day 42, as assessed by the site raters.

MADRS comprises 10 items; each item is rated on a 0–6 scale with anchors at 2-point intervals

\[
\text{MADRS total score} = \text{sum of all 10 items}
\]

If any item score is missing, then the MADRS total score will be set to missing.

A higher MADRS total score indicates a greater pathology.

The change from baseline of MADRS total score at Day 42 will be calculated as the total score at Day 42 minus the total score at baseline. A negative change from baseline in MADRS total score indicates improvement.
### 4.4.1.2 Hypothesis Testing

For the primary endpoint the following hypotheses will be tested:

\[ H_0: \text{The mean reduction in total MADRS score at Day 42 in both dose groups are} \]
\[ \mu_{RO1} = \mu_{Placebo} = \mu_{RO2} \]
\[ \text{same as in the placebo group} \]
\[ \text{versus} \]
\[ H_1: \text{At least in one dose group the mean reduction in total MADRS score at Day 42 is different from the placebo group} \]
\[ \mu_{RO1} \neq \mu_{Placebo} \text{ or } \mu_{RO2} \neq \mu_{Placebo} \]

For each dose group i=1,2 the following hypotheses will be tested:

\[ H_{0i}: \text{The mean reduction in total MADRS score at Day 42 in dose group i is the same} \]
\[ \text{as in the placebo group} \]
\[ \mu_{ROi} = \mu_{Placebo} \]
\[ \text{versus} \]
\[ H_{1i}: \text{The mean reduction in total MADRS score at Day 42 in dose group i is different} \]
\[ \text{from the placebo group} \]
\[ \mu_{ROi} \neq \mu_{Placebo} \]

A closed testing procedure will be utilized: The overall hypothesis \( H_0 \) will be tested at the two-sided significance level \( \alpha = 0.05 \) using the Dunnett test within the MMRM analysis. If \( H_0 \) will be rejected, the elementary hypothesis \( H_{0i} \) will be tested at the two-sided significance level \( \alpha = 0.05 \) utilizing t-test within MMRM, separately for \( i=1,2 \). The closed testing procedure has a two-sided maximum family-wise error rates of 0.05.

Therefore no further adjustment for multiplicity is required.

### 4.4.1.3 Statistical Analysis Method

For the assessment of differences between each RO4917523 group and placebo with regard to the mean change from baseline in MADRS total score at Day 42, an MMRM analysis incorporating data from up to Day 42 of treatment will be used for all the data collected over time with consideration of the variance-covariance matrix of the repeated measures. This method allows a general unstructured variance-covariance matrix and will include data from patients with incomplete data from some scheduled time points.

The model

\[ y_{ijk} = \mu + \pi_k + \tau_i + (\pi \tau)_{ik} + \gamma_{ij} + \beta^* M_{ij0} + \epsilon_{ijk}, \]
\[ i=1,2,3, j=1,...,n_i, k=1,7,...,35,42 \]

will include the change from baseline in MADRS total score \( y_{ijk} \) of subject \( j \) in the treatment group \( i \) at visit day \( k \) as the dependent variable. The fixed effects in the model will include the independent variables the overall mean \( \mu \), of the fixed categorical effects of treatment \( \tau_i \), assessment day relative to the first dose of randomized study drug (i.e., time) \( \pi_k \), treatment-by-time interaction \( (\pi \tau)_{ki} \), geographical region \( \gamma_{ij} \), along with the baseline MADRS total score as a covariate \( \beta^* M_{ij0} \). Time will be treated as a repeated variable within a patient. The individual within-patients residual vectors \( \epsilon_{ij} = (\epsilon_{ij1},..., \epsilon_{ij,42}) \) are assumed to be independently normal distributed with identical unstructured variance-covariance matrix. Patient, treatment, and time will be treated as factor
variables. The Restricted Maximum Likelihood (REML) method will be used for estimating the variance components. Denominator degrees of freedom will be estimated using Satterthwaite’s approximation.

A treatment-by-time interaction contrast (i.e., pairwise treatment group contrast at Day 42) will be constructed to estimate the difference between each of the RO4917523 doses versus placebo in the mean change from baseline to Day 42. Based on the analysis above, least square means, standard errors, the 95% confidence intervals (CIs) of the treatment difference, and p-values of t-test and Dunnett test will be reported for each comparison.

The MADRS total score and the change from baseline in MADRS total score at each scheduled visit will be summarized using descriptive statistics for each treatment group.

**4.4.1.4 Adjustment for Multiple Testing**

The adjustment for multiple testing is incorporated into the hypothesis testing in Section 4.4.1.2.

**4.4.2 Secondary Efficacy Endpoints**

**4.4.2.1 Definition of Secondary Efficacy Endpoints**

The secondary efficacy variables include the following:

- **Change from baseline in the CGI-S rating score at Day 42.**
  - The CGI-S is rated on a 1–7 scale. Ratings are based on degree of severity. A CGI-S score of 1 refers to “normal” and a score of 7 refers to “most severely ill.”

- **Distribution of the Clinical Global Impression of Improvement (CGI-I) rating score at Day 42.**
  - The CGI-I is rated on a 1–7 scale. Ratings are based on the degree of improvement. A CGI-C score of 1 refers to “very much improved” and a score of 7 refers to “very much worse.”

- **Frequency of patients exhibiting remission, as defined by a MADRS total score of ≤10 at Day 42.**

- **Frequency of patients exhibiting response, as defined by a MADRS total score at Day 42 ≤50% of the baseline score.**
  - The percentage of the score at Day 42 relative to the baseline score is calculated as (MADRS total score at Day 42) / (MADRS total score at baseline) *100%

- **Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16) change from baseline to Day 42.**
  - QIDS-SR16 is comprised of 16 items. Each item is scored on a 4-point anchored scale, representing least severe (0) to most severe (3).
• Patient Global Impression of Improvement (PGI-I) score at Day 42.

The PGI-I is rated on a 1–7 scale. Ratings are based on the degree of improvement. A PGI-I score of 1 refers to “very much improved” and a score of 7 refers to “very much worse.”

4.4.2.2 Analysis Methods of the Secondary Efficacy Endpoints

There will be no formal statistical analysis for secondary efficacy endpoints.

Continuous Variables

The secondary efficacy variable QIDS will be analyzed using the MMRM method described in Section 4.4.1.3 for the primary efficacy variable and the analysis of covariance (ANCOVA) described in Section 4.4.3 for the key exploratory endpoint.

Categorical Variables

Ordered categorical variables, such as change in CGI-S, CGI-I, and PGI-I, all at Day 42, will be analyzed using Wilcoxon’s rank test. For CGI-I, PG-I, and change in CGI-S, the MMRM method described in Section 4.4.1.3 will be performed as an additional, approximative analysis. For CGI-I, no baseline variable will be used as a covariate.

Binary data, such as remissions and responders, will be analyzed using Fisher’s exact test.

The values, frequencies, and changes from baseline in the secondary efficacy variables, if applicable, at each scheduled visit will be summarized using descriptive statistics for each treatment group.

Given the exploratory nature of the secondary efficacy variables, adjustment for multiple comparisons will not be applied to any of the secondary efficacy variables.

The analysis for categorical data will be applied to the observed data and last observation carried forward values (Section 4.8), except for the MMRM analyses.

4.4.3 Exploratory Efficacy Endpoints

The key exploratory endpoint is:

• Change in the MADRS total score from baseline to Day 42 for exploratory evaluation.

The other exploratory endpoints are:

• Frequency of patients who meet MADRS responder criteria (see Section 4.4.2.1) plus CGI-I score of 1) “very much improved” or 2) “much improved” at Day 42

• Frequency of patients who meet MADRS remission criteria (see Section 4.4.2.1) plus CGI-I score of 1) “very much improved” or 2) “much improved” at Day 42
• Cambridge Neuropsychiatric Test Automated Battery (CANTAB®) Cognitive Test
  Battery subset
  A subset of the CANTAB computerized battery provided by Cambridge Cognition™ will be used to assess function in the domains memory, attention, executive function and speed of processing: Motor Control Task (MOT), Rapid Visual Processing (RVP), Delayed Match to Sample (DMS), Emotional Recognition Task (ERT), Paired Associates Learning (PAL), the Stockings of Cambridge (SOC, at screening) or the One-Touch Stockings of Cambridge (OTS, at subsequent visits), and Attention Shifting Test (AST).
• Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF).
  Q-LES-Q-SF is a 16-item short form of a 60-item full version. Each item is scored from 1 for “Very Dissatisfied” to 5 for “Very Satisfied.”
• Sheehan Disability Scale (SDS)
  SDS is a combination of three self-rated items using 10-points scales for impairment at 1) work or school, 2) social life or leisure activities, and 3) home life or family responsibilities.
• Change in the MADRS total score from baseline to Days 3, 7, 11, 14, 21, 28, and 35.
  The key exploratory endpoint will be assessed at Day 42 by ANCOVA using the last observation carried forward (LOCF) method as exploratory analysis. The model will include the baseline measure as covariate, and the categorical variable treatment. The effect size of each dose compared to placebo and its 90% CI will be calculated using estimates from the treatment contrasts. The results will be used for internal decisions regarding future research in the project.
  Change in MADRS score from baseline to different visits during the treatment period except Day 42 will be analyzed using the model described above for the key exploratory variable. The LOCF method will be used.
  The exploratory variables Q-LES-Q-SF and SDS will be analyzed using the MMRM method described in Section 4.4.1.3 for the primary efficacy variable.
  CANTAB and speed of onset will be summarized descriptively.
  Binary data, such as remissions + CGI and responders + CGI, will be analyzed using Fisher’s exact test.
  The values, frequencies, and changes from baseline in the secondary efficacy variables will be summarized using descriptive statistics for each treatment group.
4.4.4 Sensitivity Analyses

4.4.4.1 Effects on Covariates
To assess effects of relevant covariates (baseline MADRS score and geographic region/country) on the outcome of the primary efficacy variable, analyses of interaction effects will be performed.

The interaction effects of treatment-by-baseline score and treatment-by-geographic region/country of the study centers will be assessed at Day 42 using ANCOVA. A model including main effects of treatment, the covariate, and the treatment-by-covariate interaction term will be used. The statistical significance of the interaction terms will be assessed at the 0.10 $\alpha$ level for the homogeneity of the treatment effect across the baseline value or the geographic region/country of the study centers. If a significant interaction effect is noted, the nature of the interaction (e.g., quantitative or qualitative) will be examined using descriptive summaries of the data by various levels of the baseline value or by geographic region/country.

4.4.4.2 Missing Data Assumptions
The analysis on the assumptions for missing data will only be performed for the primary efficacy endpoint. The primary analysis assumes a missing at random (MAR) missing-data mechanism (i.e., the probability that missing data are dependent on other observed variables, but not on the missing data itself. The assumption of MAR will be assessed by the following data review. However, it will not be possible to completely rule out the “missing not at random.”

- Comparison between treatment groups regarding dropout rates and time of dropouts
- Comparison between subsequent dropouts versus those who remained in the study regarding outcome of the primary efficacy variable at each assessment week

The random-effects pattern-mixture model will be applied as a sensitivity analysis to explore the robustness of the MMRM results of the primary efficacy variable [1].

In the random-effects pattern-mixture model, the effects of missing data patterns will be included as explanatory variables in the MMRM analysis to assess whether treatment effects vary by dropout status. For example, patients will be classified into separate patterns based on dropout status, such as dropouts, potential split into sub-groups based on the timing of the dropout, or by type of dropout, and completers. This patient-level variable and interaction terms with this variable will then be included in the primary analysis model of MMRM to assess their influence on the longitudinally observed outcome of the primary efficacy variable. The MMRM model incorporating the pattern-mixture approach will include fixed terms of status of dropout and its two-way interaction terms (i.e., dropout-by-treatment, dropout-by-assessment time), and the three-way interaction term (dropout-by-treatment-by-assessment time). The MMRM model will enable the evaluation of whether study treatment effects are consistent across
different patterns of missing data. The overall estimate of treatment effects will be compared with the estimates from the main model not including pattern mixture.

In the random random-effects pattern-mixture analysis, the statistical significance of the interaction terms will be assessed at the 0.10 significance level. If a significant interaction is noted the following sensitivity analyses are performed including a multiple-imputation analysis to evaluate the sensitivity of not MAR scenarios.

For the multiple-imputation analysis, it will be assumed that majority of missing data will be monotone due to early withdrawals (observations for all visit after a missing observation are missing). PROC MI in SAS with the Markov chain Monte Carlo (MCMC) method will be used for multiple imputations using a pattern mixture model as follows: All monotone missing data (missing observation[s] followed by non-missing observation at a later visit) will be imputed assuming that they follow the same model as other patients in the same treatment group. Monotone missing data will be imputed under the assumption that the patients who discontinued their treatment will follow the same pattern of disease evolution as patients in the placebo group. The imputation will be performed in a stepwise process for each visit: All placebo patients and those who drop out at a given visit will be included to impute the missing values of those who discontinued.

A completer analysis will be performed including only patients who have completed Day 42.

### 4.4.5 Subgroup Analyses

Subgroup analyses of the primary efficacy variable will be performed for subgroups defined by stratification factors at randomization and clinically relevant factors at baseline as follows:

- Sex: male versus female
- Geographic region: Europe versus United Stated versus Latin America versus Japan; and Japan versus non-Japan
- Class of antidepressant co-medication (SSRI vs. SNRI)
- Number of prior treatment failures (i.e., 1, 2, or 3)
- Single episode versus recurrent major depressive disorder
- Length of current episode (≤ 1 year vs. > 1 year)

The MMRM model described in Section 4.4.1.3 will be modified by adding the categorical effect subgroup (if not already in the model) and replacing the treatment effect by treatment nested in subgroup, both as effect on its own and as part of the treatment-time interaction.
For the comparison of Japan versus non-Japan, the MMRM analysis will be performed separately for each of the two subgroups.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

4.5.1 Population Pharmacokinetic Analysis

All patients with at least one adequately documented PK sample will be included in the population PK analysis.

Nonlinear mixed-effects modeling (with software NONMEM®) will be used to analyze the dose-concentration–time data of RO4917523. Population and individual PK parameters (e.g., apparent plasma clearance [CL/F] and apparent volume of distribution at steady state [Vss/F]) and their variability will be estimated. The influence of various covariates (e.g., age, sex, body weight, BMI, race) on these PK parameters will be investigated.

The data collected in this study may be pooled with data from other studies with RO4917423 PK measurements, as appropriate. Secondary PK parameters e.g., area under the plasma concentration–time curve [AUC], steady-state concentration [Css]) will be derived from the individual post-hoc predictions. Details of the analyses will be described in the Modeling and Simulation Analysis Plan before the database lock.

The results will be reported in a document separate from the CSR.

4.6 BIOMARKER ANALYSIS

For each of the single nucleotide polymorphisms (SNPs) cytochrome P450 variant 1A2 gene (CYP1A2), serotonin 2A receptor (HTR2a), serotonin transporter (SLC6A4), metabotropic glutamate receptor 5 (GRM5), and brain derived neurotropic factor (BDNF), an MMRM analysis will be performed using the models described in Section 4.4.5, where the SNP allelic results are used as subgroups. Race will be added as fixed categorical covariable. The genotypic model will be based on additive inheritance where genotype will be treated as a three-level categorical variable (-1, 1, 0). For the rs6265 SNP in BDNF, corresponding to Val66Met, the patients will be classified according to genotype distribution under a dominant model of inheritance and thus comparing Val/Val homozygotes versus Met carriers (Val/Met and Met/Met group).

4.7 SAFETY ANALYSES

For all safety variables collected by visit, the definitions of the baseline and time window will be the same as those for efficacy variables.

All safety variables will be summarized using descriptive statistics by treatment group for the safety population.

Safety variables include:

• Exposure to study drug
• AEs
• Columbia-Suicide Severity Rating Scale (C-SSRS) assessments
• Clinical laboratory tests
• Vital sign and body weight assessments
• Physical examinations
• ECG assessments
• Brief Psychiatric Rating Scale (BPRS) assessments
• Young Mania Rating Scale (YMRS) assessments

4.7.1 Exposure to Study Drug
The following extent of exposure to study drug will be summarized by treatment group:

• Duration of treatment, which will be calculated from the first day of the double-blind study medication to the last day of study treatment (i.e., the date of the last dose minus the date of the first dose plus 1).

• Extent of compliance to the prescribed treatment. The percentage of compliance for each patient will be calculated as “sum of total number of capsules taken” divided by “sum of total number of capsules expected to be taken,” then multiplied by 100. The “total number of capsules expected to be taken” will be calculated as the duration of treatment multiplied by 2 (due to two capsule prescribed per day).

4.7.2 Adverse Events
For each AE recorded, the term entered by the investigator describing the event (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) based on the MedDRA. All data displays of AEs will be performed using the system organ class (also referred to as Body System) and preferred terms. All AEs with all occurrences will be listed by patient and will contain preferred terms and comments for each event. For summaries of AE incidences, patients who experienced the same event on more than one occasion will be counted once in the calculation of the event frequency at the highest intensity reported. Each table will also present the overall number of patients experiencing at least one AE and the total number of AEs reported. In summary tables, the AEs will be sorted by body system (in decreasing order of overall incidence), then by preferred term (in decreasing order of overall incidence). A glossary of superclass terms, preferred terms, and verbatim terms will be prepared.

All AEs will be summarized by treatment group for the following analysis periods separately:

• Screening period: includes the serious AEs (SAEs; caused by protocol-mandated procedures) for which the onset date is before the day of the start of the study medication. Pre-existing conditions and AEs with start date prior to study drug administration will be considered baseline signs and symptoms (medical history).
• **Treatment period:** includes (a) the AEs for which the onset date is on or after the first day of the study drug and on or prior to the last dose day; OR (b) the AEs for which the onset date is prior to the first dose day with the end date on or after the first dose day or is unresolved and the most extreme intensity started during the treatment period.

• **Follow-up period:** includes the AEs of which onset date is after the last dose day.

The following rules will be applied for AEs with missing onset and/or end dates:

- Events that are missing both onset and end dates will be considered treatment emergent, given that a patient had at least one dose of study drug.
- If the onset date is missing and the end date is on or after the first dosing date or unresolved or missing, then the event will be considered treatment emergent.
- If the end date is missing and the onset date is on or after the first dosing date, then the event will be considered treatment emergent.
- If the end date is missing and the extreme intensity is worse than the initial intensity and the onset date is prior to the first dosing date, then the event will be considered treatment emergent.
- The duration will be set to missing.

Summaries will also be done by intensity and relationship to study drug as assigned by the investigator.

In the summary table of AEs by intensity, if a patient has more than one occurrence of an event, the event with the most severe intensity will be counted. If the intensity of an AE is missing, then the AE will be included only in the total number of events column, and not in the count of patients with the event by intensity.

In the summary table of AEs by relationship to study treatment, if a patient has more than one occurrence of an event, the most closely related event will be counted. If the relationship of an AE is missing, then the AE will be included only in the total number of events column, and not in the count of patients with the event by relationship.

All SAEs, AEs that led to death, and AEs that led to withdrawal of study treatment will also be summarized by treatment group.

The listing of patients who prematurely withdrew due to AEs will include all AEs (not only the events leading to withdrawal) that were reported by the patient.

In addition, for suicidality and severe liver injury Standardized MedDRA Query (SMQ) will be used to identify the events that may not be reported as AEs of special interest by the investigator. The AEs of suicidality will be identified by the MedDRA basket suicide/self-injury (SMQ 20000037 Narrow). The AEs of severe liver injury will be identified by a MedDRA basket to be defined.
Further analysis of AEs (e.g., temporal relationship between duration of treatment and the AE) may be conducted in case some AEs that require special attention are observed.

For any SAE with the outcome of death, patient listings will be generated containing all details, including autopsy findings, recorded on the patient AE or Additional Observations eform.

4.7.3 **Suicidality Assessment**

The items of the C-SSRS will be summarized and presented in a data listing. The number and percentage of patients will be summarized for each suicidality ideation or behavior (i.e., those marked “yes”) by study treatment and scheduled assessment week starting at randomization.

4.7.4 **Laboratory Data**

Results of all laboratory tests collected will be summarized for each assessment week using descriptive statistics for the actual and change from baseline values.

Incidence of marked abnormal laboratory test results will be summarized by treatment group based on the Roche COG 3007 definition.

4.7.5 **Vital Signs and Weight**

Vital signs (blood pressure and pulse) and weight are measured throughout the study. Summaries for vital signs will be presented at each scheduled assessment visit using descriptive statistics.

The number and percentage of patients with abnormal changes in the vital signs measures will be summarized at each scheduled assessment visit and any time during the treatment period and follow-up period, respectively, based on the following criteria:

<table>
<thead>
<tr>
<th>Vital Signs Parameter</th>
<th>Abnormality Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Percent increase $\geq 20%$ from baseline</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>Percent decrease $\geq 20%$ from baseline</td>
</tr>
<tr>
<td>Weight</td>
<td>Percent increase $\geq 7%$ from baseline</td>
</tr>
<tr>
<td></td>
<td>Percent decrease $\geq 7%$ from baseline</td>
</tr>
<tr>
<td></td>
<td>Percent increase $\geq 14%$ from baseline</td>
</tr>
<tr>
<td></td>
<td>Percent decrease $\geq 14%$ from baseline</td>
</tr>
</tbody>
</table>

In addition, orthostatic changes in blood pressure or pulse rate will be summarized. Orthostatic changes in blood pressure or heart rate are defined as the occasions when the measurements, upon moving from supine to standing position, fulfilled the following criteria based on the American Academy of Neurology’s consensus statement (1996).

- Decrease in diastolic blood pressure $\geq 10$ mmHg, or
- Decrease in systolic blood pressure $\geq 20$ mmHg, or
• Increase in heart rate ≥ 20 beats/minute

Summary of number and percentage of patients meeting the criteria will be presented for each assessment visit and any time during the treatment period and follow-up period, respectively. A listing of patients with orthostatic changes will be presented.

4.7.6 Physical Examinations

Physical examination findings (i.e., normal/abnormal) will be summarized for all patients who have a baseline and Day 42 (end-of-treatment) assessment using descriptive statistics.

4.7.7 ECGs

Actual values and change from baseline values of each parameter will be summarized using descriptive statistics for each scheduled assessment visit.

The number and percentage of patients with abnormal PR or QRS intervals, QT interval corrected using Bazett’s formula (QTcB), or QT interval corrected using Fridericia’s formula (QTcF) will be summarized for each scheduled assessment visit and at any time during the study (including follow-up) based on criteria in Table 2.

| Table 2 Adult Normal Ranges for ECG Listings and Summary Tables |
|-----------------|-------|------|
| Heart Rate ECG (bpm) | 40 | 100 |
| PR (msec) | 120 | 200 |
| QT (msec) | 200 | 500 |
| QRS (msec) | 80 | 120 |
| RR (msec) | 600 | 1500 |
| QTcB (msec) | 300 | > 450 |
| | | > 480 |
| | | > 500 |
| Increase of > 30 from baseline |
| Increase of > 60 from baseline |
| QTcF (msec) | 300 | > 450 |
| | | > 480 |
| | | > 500 |
| Increase of > 30 from baseline |
| Increase of > 60 from baseline |

QTcB = QT interval corrected using Bazett’s formula; QTcF = QT interval corrected using Fridericia’s formula.

4.8 MISSING DATA

For all rating scales, if any item score contributing to the total/factor/subscale score is missing, then the total/factor/subscale will be set to missing.
The main analysis of the primary and secondary continuous efficacy variables will be performed using a mixed-effects model, and no imputation for missing data will be applied. All observed assessments up to Day 42 will be included in the MMRM analyses.

For the supportive efficacy analysis using the ANCOVA model and the categorical data analysis, as an exploratory analysis to assess the robustness of the results, analyses of the ITT population will be repeated using the LOCF replacement for missing values. The LOCF dataset includes data recorded at a given visit or, if no observation was recorded at that visit, data carried forward from the previous post-baseline visit. To perform an efficacy analysis at Day 42, the last observed post-baseline value up to 6 days after the last dose day of patients who dropped out of the study before Week 6, whether scheduled or unscheduled, will be carried forward to Week 6. Baseline data will not be carried forward or averaged with post-treatment data to impute missing values for the LOCF dataset.

To understand the pattern of missing data observed during the study and, thus, the missing data mechanism, the following data will be summarized:

- Timing of discontinuations by treatment group
- Reasons for discontinuation by treatment group and time
- Mean of the primary efficacy variable of those who dropped out versus those who remained at each scheduled assessment week. The dropout cohort at each assessment week will include the patients who had their last primary efficacy assessment in the corresponding week interval.

Sensitivity analyses for the influence of the missing-data mechanism are described in Section 4.4.4.2.

No imputation will be applied for missing data of safety variables.

4.9 INTERIM ANALYSES

No interim analyses are planned for this study.

5. REFERENCES


Appendix 1
Protocol Synopsis

SYNOPSIS OF PROTOCOL NUMBER NP25620

TITLE
• A randomized, double-blind, parallel-group study of the safety and efficacy of RO4917523 versus placebo, as adjunctive therapy in patients with major depressive disorder with inadequate response to ongoing antidepressant treatment.

SPONSOR
F. Hoffmann-La Roche Ltd

INDICATION
Major Depressive Disorder (MDD)

OBJECTIVES
Primary
• To evaluate the efficacy of two fixed doses of RO4917523 compared to placebo in a confirmatory manner over 6 weeks as adjunctive therapy in patients with MDD with inadequate response to ongoing antidepressant treatment, based on mean change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

Secondary
• The secondary objectives are to evaluate change after 6 weeks of treatment with RO4917523 versus placebo as adjunctive therapy on the following:
  • Clinical Global Impression Scores: Severity (CGI-S) from baseline to end of treatment, and Improvement (CGI-I) at end of treatment
  • Safety and tolerability of RO4917523
  • Proportion of patients exhibiting remission (a MADRS score of less than or equal to 10)
  • Proportion of patients exhibiting response (reduction in MADRS score equal to or greater than 50% of the baseline score)
  • Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16)
  • Patient Global Impression of Improvement (PGI-I) score at end of treatment

Exploratory
• Key Exploratory Objective
  • To evaluate the effect size (ES) of two fixed doses of RO4917523 compared to placebo over 6 weeks as adjunctive therapy in patients with MDD with inadequate response to ongoing antidepressant treatment, based on mean change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

• Other Exploratory Objectives
  To investigate the differential effect of RO4917523 vs. placebo in:
  • Proportion of patients who meet MADRS responder criteria plus CGI-I score of 1) “very much improved” or 2) “much improved”
• Proportion of patients who meet MADRS remission criteria plus CGI-I score of 1) “very much improved” or 2) “much improved”
• Speed of onset of antidepressant effect based on change over time in any of the depression symptom scales
• CANTAB Cognitive Test Battery subset
• Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)
• Sheehan Disability Scale (SDS)

• Pharmacokinetics
  • Pharmacokinetics of RO4917523 in the target population with the objective of performing a population pharmacokinetic analysis with non-linear mixed effect model

• Biomarkers
  • Identify biomarkers that are predictive of response to RO4917523 treatment
  • Increase our knowledge and understanding of the pathogenesis, course and outcome of depression and related diseases
  • Develop biomarker or diagnostic assays, and establish the performance characteristics of these assays

TRIAL DESIGN
• This is an outpatient trial consisting of three consecutive periods: screening (up to 14 days), 6-week double-blind treatment, and a 21 day follow-up period.

NUMBER OF SUBJECTS
Approximately 300 patients, randomized in equal proportions to the three treatment arms.

TARGET POPULATION
• The study will include male and female outpatients from 18 to 70 years of age with a primary diagnosis of major depressive disorder (MDD) without psychotic features as defined by DSM-IV-TR criteria, and having inadequate response to ongoing antidepressant therapy. Patients must have had at least one but no more than three treatment failures (of adequate dose and duration according to the Massachusetts General Hospital Antidepressant Treatment History Questionnaire [MGH ATRQ]). Failure to ongoing antidepressant treatment in the current episode is counted as one treatment failure.

LENGTH OF STUDY
• 14 day screening period
• 6 week double-blind treatment
• 21 day follow-up

END OF STUDY
The date of the last visit (including the follow-up period) of the last patient in the study

INVESTIGATIONAL MEDICAL PRODUCT(S)
• Doses of RO4917523 0.5 mg or 1.5 mg supplied as pellets in capsules, in combinations of Ro 491-7523/F18 0.5 mg, Ro 491-7523/F19 1.0 mg, taken orally once a day
Comparative "Drug"

DOSE / ROUTE / REGIMEN

Matching capsules of placebo Ro 491-7523/F21, taken orally once a day.

ASSESSMENTS OF:

- EFFICACY
  - MADRS total score
  - Remission (a MADRS score less than or equal to 10)
  - Response (reduction in MADRS score equal to or greater than 50% from baseline)
  - CGI-S
  - CGI-I
  - PGI-I
  - QIDS-SR16
  - Q-LES-Q-SF
  - SDS
  - CANTAB

- SAFETY
  - Adverse events (AEs) and concomitant medications will be monitored throughout the entire study (screening through follow-up). Intensity of AEs will be graded on a 3 point scale (mild, moderate, or severe)
  - A subscale (4 items) of the BPRS will be completed only to follow up on treatment emergent psychotic-related and mania-related (mania or hypomania) adverse events. The symptom constructs included are conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content
  - The YMRS (item 1 only for mood elevation) will be completed only to follow up on treatment emergent psychotic-related and mania-related (mania or hypomania) adverse events
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Physical examination
  - Vital signs (pulse, blood pressure)
  - 12-lead ECG
  - Laboratory parameters
    - Chemistry panel
    - Hematology panel with differential
    - Free T4 and TSH
    - Viral Serology
    - Urinalysis (dipstick)
    - Urine drug screen
    - Pregnancy test in females
  - Data Safety Monitoring Board (DSMB)
    - An independent Data Safety Monitoring Board (DSMB) will review potential safety signals of concern. The DSMB will be composed of non-sponsor members who are not involved in the conduct of this study. The DSMB will review available safety data from this trial at regularly scheduled intervals as
-EXPLORATORY BIOMARKERS (non-inherited)

PK sampling will be obtained from all patients according to the Schedule of Assessments.

Specimens for the Roche Clinical Repository (RCR) will be collected for dynamic (non-inherited) biomarker discovery and validation. The RCR sampling is optional. Blood specimens will be collected as per Schedule of Assessments, with details as follows:

- **Plasma and Serum assays**: Blood samples for plasma and serum isolation will be obtained at baseline and the end of treatment. A total of 4 samples (2x6 mL for serum and 2x6 mL for plasma; 24 mL total) for each patient will be collected during the study. These samples will be used for biomarker assays for candidate depression biomarkers.

- **Blood for RNA expression profiling**: Blood samples for RNA isolation will be obtained at baseline and the end of treatment (5 mL each; 10 mL total).

- **Blood sample for epigenetic analysis**: Blood samples for DNA isolation will be collected at baseline and the end of treatment (6 mL each; 12 mL total).

These specimens will be stored for up to 15 years after the end of the study.

-EXPLORATORY BIOMARKERS (inherited)

Additional specimens for the Roche Clinical Repository (RCR) will be collected from consenting patients for genetic biomarker (inherited) discovery and validation. The RCR sampling (inherited) is optional. A single blood specimen will be collected from consenting patients, with details as follows:

- **Blood sample for genetic analysis**: A blood sample (approx. 6 mL) for DNA isolation will be collected at a single study visit as per Schedule of Assessments. If however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected at any time (after randomization) during the conduct of the clinical study. The sample may be processed using techniques such as sequencing or microarray profiling.

These specimen(s) will be stored for up to 15 years after the end of the study.

-MANDATORY BIOMARKERS (MB)

Blood samples for serum and plasma protein biomarker discovery and validation will be collected from all patients where permissible with local regulations at baseline and the end of treatment. A total of 4 samples (2x6 mL for serum and 2x6 mL for plasma; 24 mL total) for each patient will be collected during the study. These specimens will be destroyed no later than 5 years after the end of the study.

- CLINICAL GENOTYPING (CG)

A 3 mL whole blood sample will be taken for DNA extraction from all patients where permissible with local regulations at baseline. The DNA will be tested for one or more of the following specific genes: the cytochrome P450 variant 1A2 gene (CYP1A2), the metabotropic glutamate receptor 5 (GRM5), the serotonin 2A receptor (HTR2A), the serotonin transporter (SLC6A4), and brain derived neurotropic factor (BDNF). This specimen will be destroyed immediately after the analysis has been completed.
PROCEDURES (summary): Screening Period (up to 14 days)

During the screening period, informed consent will be obtained, and the investigator will determine whether the candidate meets all inclusion criteria and does not meet any exclusion criteria.

6-Week Double-blind Treatment Period

In order to be randomized into the double-blind treatment period, patients must have at baseline:

- No significant risk of suicidal behavior (e.g., consider the Suicidal Ideation section of the C-SSRS “Since Last Visit” for this evaluation)
- No significant change in medical or psychiatric condition, or change in medications since screening (unless agreed with the Sponsor/Medical Monitor)
- Negative result on the Baseline pregnancy test (if applicable)
- No change in ongoing antidepressant therapy, and ability to continue for the duration of the double-blind treatment period without modification to the dosing schedule
- An ESF/EAF approved by the Sponsor/Medical Monitor

The double-blind treatment period begins with the investigational site call into IVRS confirming the patient’s eligibility. The patient will be randomized and receive their first dose of study medication on Day 1.

Dose 1 of the blinded study medication is to be administered in the clinic immediately after a meal and before 12 pm (noon), or soon thereafter upon consultation with the Sponsor/Medical Monitor, once all baseline procedures and assessments are completed. Patients will remain at the clinic for 6 hours after the first dose for safety monitoring and for the PK samples (according to clinical observation and patient availability). Subsequently, dosing will be once daily in the morning immediately after breakfast.

As with any experimental drug at this stage of development, it is advisable for patients not to drive or operate dangerous machinery until known side effects (e.g., dizziness and somnolence) can be adequately assessed on an individual basis during the trial.

Patients will arrive at each study visit without having taken their daily dose of study medication, and site staff will record the time of their last dose. Following collection of the pre-dose PK blood sample (if applicable) and a meal, patients will take their next dose of study medication before 12 pm (noon) or soon thereafter upon consultation with the Sponsor/Medical Monitor. The last dose of study medication will be administered on Day 42 (End-of-Treatment visit).
Early Discontinuers will be instructed to return as soon as possible for the End-of-Treatment visit, and 21 days later for the Follow-up visit.

**Follow-up Period (21 days)**

A Follow-up Visit will take place 21 days after the End-of-Treatment visit. During the follow-up period, adjustments to antidepressant treatments may be initiated if deemed necessary by the investigator.

**STATISTICAL ANALYSES:**

Main efficacy analysis will be performed in a confirmatory manner based on ITT population, using a mixed effects covariance pattern model (MMRM) to utilize all the data collected over time. A closed testing procedure will be used to take multiple comparisons into account. As supporting analysis, the analysis may be repeated on the per-protocol population. Another supportive analysis will use an ANCOVA with LOCF imputation for missing data. The primary efficacy variable is change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

All safety variables (e.g., adverse events, lab tests, ECG, vital signs, BPRS, YMRS, ASEX) will be summarized for each assessment time (including follow-up) using descriptive statistics. The items of the C-SSRS will be presented by individual listings and the outcomes from this scale will be classified using the C-CASA methodology.