Official Title: A Phase IIb, Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Tolerability of Basmisanil (RO5186582) as Adjunctive Treatment in Patients With Cognitive Impairment Associated With Schizophrenia Treated With Antipsychotics

NCT Number: NCT02953639

Document Date: Protocol Version 5: 31-July-2018

PROTOCOL

TITLE:	**A PHASE IIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF BASMISANIL (RO5186582) AS ADJUNCTIVE TREATMENT IN PATIENTS WITH COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA TREATED WITH ANTIPSYCHOTICS**
PROTOCOL NUMBER:	BP39207
VERSION:	5
P-IND NUMBER:	130290
TEST PRODUCT:	Basmisanil (RO5186582)
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 7 July 2016
DATES AMENDED:	Version 2: 21 September 2016 Version 3: 11 April 2017 Version 4: 28 November 2017 Version 5: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	31-Jul-2018 18:51:28

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE IIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF BASMISANIL (RO5186582) AS ADJUNCTIVE TREATMENT IN PATIENTS WITH COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA TREATED WITH ANTIPSYCHOTICS**
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P-IND NUMBER:	130290
TEST PRODUCT:	Basmisanil (RO5186582)
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol BP39207 has been amended to incorporate the following changes:

- Clarification of positive Hepatitis B serology test results at screening (Section 4.2.3 Exclusion Criterion #9 and laboratory assessments Section 4.6.1.6).

  As described in File Note #7 dated 14 March 2018, a positive result at screening for hepatitis B (HBV) is an exclusion criterion. Patients with a positive result for Hepatitis B surface antigen (HBsAg +) at screening are not eligible for this study, as the study participant presents an active form of the disease and is infected. Results for hepatitis B core antibody (HBcAb) included in laboratory tests at screening inform about medical hepatitis B history. Positivity for anti-HBc (HBcAb +) together with a negative HBsAg (HBsAg -) points towards an immune signature due to natural infection and therefore such patients can be enrolled unless there is evidence of a clinically significant hepatic disorder at screening as per investigator assessment.

  Therefore, the test result for total hepatitis B core antibody (HBcAb) does not contribute to determination of eligibility but will continue to be performed for medical history purposes. This has now been clarified in the laboratory assessments section (Section 4.6.1.6).

- Clarification of exclusionary ALT/AST/bilirubin results (Section 4.2.3 Exclusion Criterion #8).

  As described in File Note #8 dated 5 April 2018: The formatting and syntax of the protocol have been revised to more clearly reflect that the following findings exclude patients from participation:

  – Elevated ALT and/or AST results > 2 × ULN in combination with elevated bilirubin>ULN.
  – Elevated serum creatinine > 1.5 × ULN

  The following findings do not constitute a reason to exclude patients from participation, unless considered clinically significant by the Investigator:

  – An isolated ALT and/or AST result > 2 × ULN
  – An isolated bilirubin result > ULN

- Use of saliva test for alcohol (Section 4.6.1.6)

  The protocol has been updated to show that alcohol may be tested using either urine or saliva.

- Clarification of drug panel (Section 4.6.1.6)

  As described in the File Note dated 22 May 2018, participants who test positive for the following 6 drugs are excluded from the study (opiates, amphetamines, cocaine, hallucinogens, PCP, cannabis). The central laboratory has provided a 14-panel urine drug screen to sites as a replacement to the 10 panel screen previously provided.

  Despite an additional 8 drugs available to test on the panel, only the results for the 6 drug classes named above will be recorded and result in exclusion of the subject if positive.

- IQ score on the Wechsler Abbreviated Scale of Intelligence (WASI-II) changed from < 70 to ≤ 65 (Section 4.2.3 Exclusion Criterion #6)

  The exclusion criterion based on the Full Scale IQ score on the Wechsler Abbreviated Scale of Intelligence (WASI-II) has been changed from < 70 to < 65 (Section 4.2.3 Exclusion Criterion #6) in order to further avoid unnecessary exclusion of patients that are capable of understanding study risks and benefits (refer to Section 4.2.2 amended inclusion criterion #2) and of participating (refer to Section 4.2.2 inclusion criterion #3).

- Addition of the evaluation to sign consent (ESC) form (Section 4.2.2 Inclusion Criterion #2, Section 4.6.2.2, Section 8.2) in order to ensure all patients enrolled fully understand the study demands, risks and benefits.

- Addition of the option of dosing by placing granules directly into the mouth followed by swallowing with water (Section 4.4.2).

  The current dosing method requiring patients to take basmisanil granules sprinkled on a small amount of soft food leads to a high burden on patients and is a major contributor to the study dropout rate. Therefore, an optional alternative dosing method has been added to the protocol whereby the patients can place the contents of the stick-packs directly into their mouth and swallow them with at least 100 mL of water. (Note: <u>the granules must not be mixed with water outside the mouth</u>).

  This alternative dosing option is supported by the available bioequivalence/food effect data (Study WP28978, see basmisanil Investigator's Brochure). [redacted]

  Current and future patients in Study BP39207 will therefore be given the option to choose between the two available dosing methods.

Additional minor changes and corrections have been made to improve clarity and consistency. Substantial new information appears in italics.

PROTOCOL AMENDMENT, VERSION 5: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

[redacted]

Section 3.1.1 Overview of Study Design

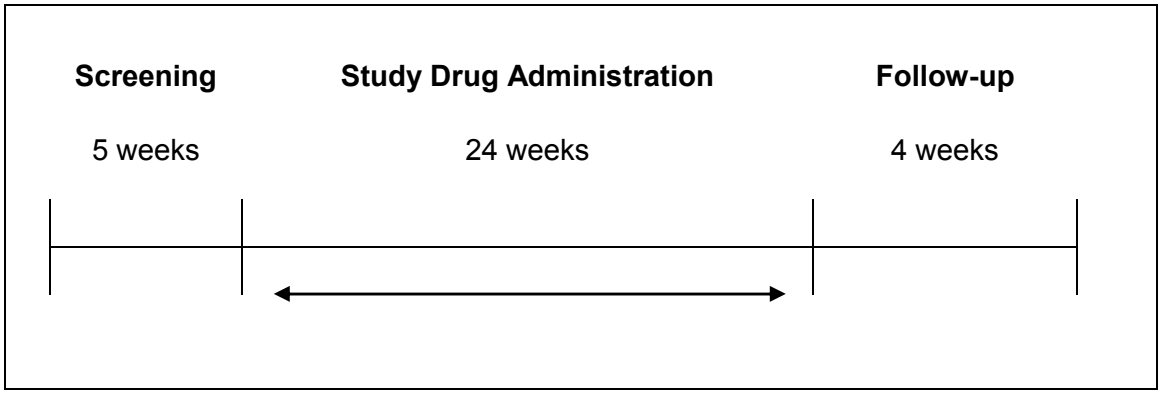
The study will be divided into 3 phases (Figure 2):

- A screening phase of approximately 5 weeks *which includes Baseline 1 and Baseline 2 visits.*
- A double-blind treatment phase *with study drug,* of approximately 24 weeks.
- A follow-up phase of approximately 4 weeks after treatment discontinuation.

Efficacy, safety, and PK assessments will be conducted throughout the study, as detailed in the Schedule of Assessments (Appendix 1).

Patients will be treated until the end of the study treatment period, unacceptable toxicities, or withdrawal of consent.

Figure 1 Study Design



The total duration of the study for each enrolled subject will be up to 34 weeks (from screening through completion of the last the last follow-up visit): 5-week Screening phase *which includes a placebo test-phase*, 24-week treatment period *with study drug*, and 4-week follow-up period.

3.1.3.2 Efficacy IMC

Once approximately 90 patients~~, with a minimum of 30 patients per treatment arm (in case the 240 mg BID dose is stopped, patients in the 120 mg BID group will be added to the count of patients in the high dose group)~~ have completed at least 12 weeks of treatment, an~~d~~ efficacy IMC (consisting of the members of the safety IMC along with the study translational medicine leader, a senior Roche clinical representative independent from the study team, a pharmacometrician, and others who will be involved in the decision-making process as needed) will conduct an interim analysis for futility on the primary endpoint of the study. The committee will review and evaluate the data unblinded at the group level (including ~~global clinical impression and changes in positive and negative symptomatology,~~ safety data and PK results if available), and the decision will be taken to either continue the study unchanged, to stop one arm or to end the study. Descriptions of the conduct of the analysis, including pre-defined success criteria for the efficacy interim analysis, are summarized in Section 6.10 and will be described in further detail in a separate Efficacy IMC Agreement Document.

4.2.2 Inclusion Criteria

1. Male or female subjects aged between 18 and 50 years.

2. Able to participate and willing to give written informed consent.

3. *Able to understand key risk and benefits of the study as demonstrated by a score ≥ 10 on the Evaluation to Sign Consent (ESC) form.*

4. Able to perform study assessments and procedures and comply with the study protocol, including one week of hospitalization/in-patient stay.

4.2.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

6. FSIQ ≤ 65~~<70~~ on the Wechsler Abbreviated Scale of Intelligence (WASI–II) at screening.

7. Any clinically relevant ECG abnormalities at screening, including an average triplicate QTcF above 450 msec.

8. Clinically significant abnormal vital signs or laboratory test results at screening.
   Specifically, for the clinical chemistry parameters:
   - the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ~~should not be >~~*exceeding* 2 ~~times~~ *fold* the upper limit of normal (ULN)~~;~~ ***in combination with*** ~~and~~ the total bilirubin > ULN with the exception of Gilbert syndrome
   - serum creatinine ~~should not~~ exceed*ing* 1.5-fold ULN.

9. Positive result at screening for hepatitis B (HBV), hepatitis C (HCV, untreated), or human immunodeficiency virus (HIV)-1 and -2. HCV patients who have been successfully treated and who test negative for HCV RNA, may be considered eligible for entry into the study. *See Section 4.6.1.6, viral serology, laboratory assessments.*

10. Concomitant use of prohibited medications (see Section 4.5.2).

11. Moderate to severe substance use disorder (other than nicotine or caffeine), as defined by the DSM-5, within the last 12 months.

12. Confirmed positive test for alcohol or drugs of abuse at screening or at baseline.

13. Failure to detect blood concentrations of the prescribed antipsychotic medication. *If*~~In case~~ no commercial test is available for recently approved antipsychotics, *the* decision will be taken on a case by case basis between the Investigator and the Roche TML (or designee).

14. Subjects with a history of poor compliance in the last 2 years.

4.4.2 Dosage and Administration

The study medication is two stick-packs taken orally, twice daily (in the morning and in the evening within 30 minutes of a meal) over 24 weeks. Granules should be mixed with or sprinkled onto a small amount soft food (i.e., yogurt, apple sauce, or pudding) and all of the food consumed ~~to ensure accurate dosing.~~ *or as an alternative, patients have the option of placing the granules directly into their mouth followed by swallowing with a glass of water. (Note: the granules must not be mixed with water before putting them into the mouth).*

On Study Day 1, the first dose of medication will be administered in the hospital or at the clinic/study center once all pre-dose assessments have been conducted and eligibility has been confirmed. For all subsequent study visits, the morning dose will be taken at the study center. The last dose of medication will be the morning dose, administered at the clinic/study center at Week 24 visit.

Patients will be provided with a sufficient amount of medication to cover study treatment until the next site visit (including some overage). The qualified individual responsible for dispensing the study drug supply will prepare the correct medication supply required as instructed by IxRS and according to the randomization schedule. This individual will write the date dispensed and Patient Number on the study drug label and on the Drug Accountability Record. This individual will also record the study drug batch or lot number received by each subject during the study.

Guidelines for treatment interruption or discontinuation are provided in Section 3.1.2 and Section 4.7.1.

4.4.3.1 Medication adherence system

The patient's capacity to comply with taking twice daily study medication will be assessed during the screening period, between Baseline 1 and Baseline 2 visits. Patients will be asked to take placebo medication and to report each intake using *a medication adherence monitoring platform ("Platform")* ~~a web-based platform/an app (~~provided on a smartphone~~)~~. A compliance report will be made available to support the PI's assessment of the patient's capacity to comply with the study requirements (refer to Section 4.2.2, "Inclusion Criteria").

~~This trial will employ a medication adherence monitoring platform ("Platform"). The Platform will either be provided to a patient pre-loaded on a smartphone, or if possible the patient may download the Platform onto their own smartphone~~. Patients will receive a medication reminder at a time within a pre-defined window to take their medication. Patients will follow a series of prescribed steps *using the front-facing camera* ~~in front of the front facing webcam~~ of the smartphone to confirm patient identity and medication to be taken. The patient has to confirm ingestion of medication manually *as well as the*

chosen dosing method (i.e., soft food vs. direct intake) as soon as the platform has been updated to include this functionality. In addition, built-in reminders and a communication system allows real-time intervention in case of non-compliance. Use of this Platform will in no way supersede or replace the physician and/or prescribed medication protocol. Because the Platform does not change the medication protocol, but rather encourages adherence, use of this Platform presents minimal risk to the patients.

4.5.1 Permitted Therapy

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter (OTC) drugs, approved dietary and herbal supplements, nutritional supplements and any non-medication interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy) used by a patient from screening until the follow-up visit. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

All medication administered to manage AEs (including extrapyramidal symptoms such as dyskinesia or akathisia) should also be recorded on the Adverse Event eCRF.

Allowed concomitant therapy, including medications used for the treatment of ~~stable~~*chronic* medical conditions other than schizophrenia that are allowed, must be on a stable dosing regimen for 6 weeks prior to screening and remain stable throughout the study (from screening to last follow-up visit. *Dose adjustments that are required as part of routine treatment to control the chronic condition (such as dose adjustments of insulin or anti-hypertensive medication) are permitted.* Any changes in antipsychotic therapy, for management of worsening of symptoms or initiation of additional pharmacotherapy including antidepressant after randomization may be permitted on a case by case basis, in consultation between the PI and the Medical Monitor/Sponsor. The reason for such changes should be appropriately documented.

4.5.2 Prohibited Therapy

[redacted]

[redacted]

Diphenhydramine

Diphenhydramine is not permitted because of potential cardiac effects.

Dofetilide

Dofetilide use is not permitted because of the potential for interaction between basmisanil and renally-cleared cationic drugs, as well as the very narrow therapeutic window of dofetilide.

Anticholinergic medications

Anticholinergic (e.g., benztropine, biperiden, or trihexyphenidyl) are prohibited during the trial due to potential negative impact on cognition and the potential to interfere with the study primary endpoint. Anticholinergics prescribed as prophylaxis treatment for extrapyramidal symptoms need to be washed-out prior to enrollment. If deemed necessary by the PI, beta blockers (e.g. propranolol) can be prescribed instead.

~~**Clozapine, Diphenhydramine, Direct oral anticoagulants (dabigatran etexilate, edoxaban, apixaban and rivaroxaban) and Colchicine**~~

~~Not permitted in this study.~~

4.6.1.5 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at time-points specified in the Schedule of Assessments (Appendix 1).

Additional ~~blood or urine~~ samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient's safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility. If there is an alternative explanation for a positive ~~urine or blood~~ test for drugs of abuse, e.g., previous occasional *and acute* intake of a medication or food containing for example, codeine, benzodiazepines or opiates, the test could be repeated to confirm washout. *Furthermore, in case of a positive test for a drug of abuse at screening, that can be explained by prescribed and permitted co-medication (see Section 4.5.1), a positive result at screening is not systematically exclusionary and will be evaluated on a case by case basis.*

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

Samples collected before dosing or from patients on placebo are to be taken as a precautionary measure and may not be analyzed in the first instance.

Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Hematology (leukocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells]).
- Serum chemistry (sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, lactate dehydrogenase [LDH]).
- Coagulation (international normalized ratio [INR], activated partial thromboplastin time [aPTT], prothrombin test [PT]).
- Viral serology
    - HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody).
    - *Hepatitis B (surface antigen (HBsAg determines HBV positivity whereas total hepatitis B core antibody (HBcAb) will be tested for but results do not contribute to eligibility assessment.)*
    - ~~Hepatitis B surface antigen (HBsAg).~~
    - ~~Total hepatitis B core antibody (HBcAb).~~
    - Hepatitis C virus (HCV) antibody. In cases where hepatitis C was successfully treated, a positive HCV serology result can be followed by HCV RNA testing
- Lipids (cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides).
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a blood or urine pregnancy test as outlined in the Schedule of Assessments (Appendix 1).
- Drug and alcohol screen:

  Urine *or saliva* drug screen will be performed at time points indicated in Appendix 1. Agents tested for are *at a minimum*: opiates, amphetamines, cocaine, hallucinogens, PCP, *and* cannabis and alcohol. An alcohol ~~breath~~ *saliva* test can be performed at any time during the study at the PIs discretion.
- Benzodiazepine assessment: Benzodiazepine levels will be measured in blood samples as described in Appendix 1 (see Section 4.5.2 on use of $GABA_A$ PAMs).

4.6.2.2 Screening and Pre-treatment Assessments

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

An Evaluation to Sign Consent (ESC) form will be used to ensure patients' understanding of the study. The form consists of 6 questions rated on a 0 to 2 scale for the level of understanding and participants are required to score at least 10 out of a possible 12 in order to participate in the study. It may be necessary to review the consent documents with the patient multiple times and repeat the ESC to ensure this degree of comprehension (maximum of 3 times).

All screening and pre-treatment assessments must be completed and reviewed to confirm that patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure.

6.3.2 Efficacy Analysis Population

Per-Protocol Population

The PP population will be precisely defined in ~~the statistical analysis plan~~*a separate document*, before database closure, as the subset of the ITT population without major protocol deviations.

6.10 Interim Analyses

An interim analysis will be conducted when approximately 30 patients per arm have completed the first 12 weeks of treatment. The analysis will be conducted by the efficacy IMC as described in Section 3.1.3.2.

This analysis will focus on the change from baseline to Week 12 in MCCB neurocognitive composite score, which will be analyzed using an MMRM model which will be similar to that described for the primary analysis (including all stratification factors although this may not be possible depending on the actual cell size). The pairwise comparison of each active dose to placebo will be evaluated using the estimated effect size based on the least-squares mean (LSM) estimates from the MMRM models. For each dose arm, the decision whether to continue or drop the arm for the remainder of the study will be based on the ~~posterior~~ *conditional* probability that the true treatment effect size for that arm is ≥ 0.35. If the calculated *conditional* ~~posteri~~ probability is less than 20% that the true treatment effect size can reach this threshold for one of the two doses, then that dose arm may be discontinued. If this *conditional* ~~posterior~~ probability is less than 20% for both dose arms, then the study may be discontinued for futility. ~~A informative prior will be used for the posterior probability calculations.~~

In case the calculated *conditional* ~~posteri~~ probability that the true treatment effect size can reach the threshold of effect size > 0.35 is more than 20% for both treatment arms, one treatment arm may still be discontinued.

Further analysis details on the interim analysis will be documented in a separate Efficacy IMC Agreement Document prior to the conduct of the interim analysis.

8.2 Informed Consent

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

In this study, the informant will be asked to provide information useful to assess patient eligibility and to complete clinician rated scales. A separate written informed consent will be obtained from the informant.

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

In this study, the Investigator or Designee shall assess the capacity of the patient to give informed consent while discussing the study and the Consent Forms. This assessment shall be confirmed by the *results of the ESC form (see Inclusion Criteria Section 4.2.2) and the* IQ measure (see Exclusion Criteria ~~#6~~*, Section 4.2.3*) done during the Screening Visit.

10 References

Investigator's Brochure, Basmisanil (RO5186582)-$GABA_A$ α5 negative allosteric modulator, Version ~~9, Addendum 1,~~*10,* ~~October 2017~~*June 2018*.

Appendix 1 Schedule of Assessments

The Schedule of Assessments has been updated to include the Evaluation to Sign Consent at Screening.

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PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIB, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF RO5186582 AS ADJUNCTIVE TREATMENT IN PATIENTS WITH COGNITIVE IMPAIRMENT**
PROTOCOL NUMBER:	BP39207
VERSION:	5
P-IND NUMBER:	130290
TEST PRODUCT:	Basmisanil (RO5186582)
PHASE:	IIB
INDICATION:	Cognitive impairment associated with schizophrenia
SPONSOR:	F. Hoffmann-La Roche Ltd.

OBJECTIVES

Primary Objectives

The primary objective of this study is:

- To investigate the efficacy of 24 weeks of basmisanil treatment on cognitive function as measured by the MATRICS consensus cognitive battery (MCCB) neurocognitive composite score, in stable patients with cognitive impairment associated with schizophrenia (CIAS) treated with antipsychotics.

Secondary Objectives

The secondary objectives for this study are as follows:

To evaluate the effect of 24 weeks of treatment with basmisanil in stable patients with CIAS treated with antipsychotics on the following:

- Individual cognitive domains of the MCCB, namely attention, speed of processing, reasoning, working memory, visual learning, verbal learning and social cognition.
- Additional specific hippocampal and prefrontal-dependent cognitive tasks and processes (as measured by the Trail making test [TMT]-B, Wechsler memory scale - Fourth edition, verbal paired associates [WMS IV-PAL] and Wechsler memory scale - Fourth edition, logical memory test [WMS IV-LM]).
- Functional capacity and performance (as measured by the Personal and Social Performance scale [PSP] and Schizophrenia Cognition Rating Scale [SCoRS]).
- To evaluate the safety and tolerability of 24 weeks of basmisanil treatment in patients with CIAS treated with antipsychotics.
- To characterize the steady-state pharmacokinetics (PK) of basmisanil and its metabolites, if appropriate, in stable patients with CIAS treated with antipsychotics using population PK modelling methods.

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To explore the effect of 24 weeks of treatment with basmisanil on semantic priming

(measured in the category fluency test of the MCCB) and primacy/recency effects (measured in the Hopkins verbal learning test of the MCCB), two experimental measures of hippocampal-dependent cognitive processes.

- To determine whether the patients' genetic profile predicts effects of treatment with basmisanil on cognitive functions.
- To evaluate the effect of 24 weeks of treatment with basmisanil on smartphone-based self-reported mood, sleep, subjective well-being and cognitive functioning.
- To evaluate the effect of 24 weeks of treatment with basmisanil on functional capacity assessed by novel computerized measures and "work readiness".
- To evaluate the effect of 24 weeks of treatment with basmisanil on symptoms of schizophrenia including positive and negative symptoms.
- To evaluate the effect of 24 weeks of treatment with basmisanil on quality of life.

STUDY DESIGN

Description of Study

This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase IIb study, to evaluate the effects of 24 weeks of basmisanil treatment in stable patients with CIAS treated with antipsychotics.

The final analysis will investigate the PK, safety and tolerability, and efficacy of 24 weeks of basmisanil treatment on cognition and functioning.

Two doses of basmisanil (240 mg, 80 mg) will be tested against placebo. Approximately 231 patients will be randomized to one of three treatment arms, in a 1:1:1 ratio:

- Arm 1: 240 mg BID (may be lowered to 120 mg BID upon Safety Internal Monitoring Committee [IMC] decision).
- Arm 2: 80 mg BID.
- Arm 3: Placebo BID.

Randomization will be stratified based on age, sex and "schizophrenia cognitive subtype". The stratification threshold for age will be $\leq$ 35 years and $>$ 35 years. The "schizophrenia cognitive subtype" will be determined at screening based on the difference between the pre-morbid intelligence quotient (IQ), estimated by the wide range assessment test (WRAT)-4 reading test standard score, and current full scale IQ score~~s~~ (FSIQ), estimated by the Wechsler Abbreviated Scale of Intelligence – second edition (WASI-II).

The study will be divided into 3 phases:

- A screening phase of approximately 5 weeks *which includes Baseline 1 and Baseline 2 visits*.
- A double-blind treatment phase *with study drug,* of approximately 24 weeks.
- A follow-up phase of approximately 4 weeks after treatment discontinuation.

Efficacy, safety, and PK assessments will be conducted throughout the study, as detailed in the Schedule of Assessments.

Patients will be treated until the end of the study treatment period, unacceptable toxicities, or withdrawal of consent.

NUMBER OF PATIENTS

A total of up to 231 patients will be enrolled in the study, to ensure that a minimum of 150 patients (50 patients per treatment arm) will have evaluable data at 24 weeks. They will be randomized 1:1:1 to the three study arms. The sample size may be increased if the actual premature withdrawal rate is higher than expected.

TARGET POPULATION

The study population consists of male and female subjects with schizophrenia aged 18 to 50 years who are on stable antipsychotic therapy.

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria

Patients must meet the following criteria for study entry:

1. Male or female subjects aged between 18 and 50 years.
2. Able to participate and willing to give written informed consent.
3. *Able to understand key risk and benefits of the study as demonstrated by a score ≥ 10 on the Evaluation to Sign Consent (ESC) form.*
4. Able to perform study assessments and procedures and comply with the study protocol, including one week of hospitalization/in-patient stay.
5. Diagnosis of schizophrenia of any type utilizing the Mini International Neuropsychiatric Interview (MINI) and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) direct clinical assessments, family informants and past medical records.
6. Evidence of stability of symptoms for 3 months at screening, i.e., without hospitalizations for schizophrenia or increase in level of psychiatric care due to worsening of symptoms of schizophrenia.
7. Schizophrenia clinical symptom severity defined by the following: Hallucinatory Behavior item score ≤ 5 and a Delusion item score ≤ 5 of the Positive and Negative Syndrome Scale (PANSS).
8. On a stable regimen of antipsychotic therapy for at least 3 months at screening and receiving no more than two antipsychotics. Antipsychotic regimen: Patients must be on a "primary" antipsychotic and may be on a secondary antipsychotic. The amount of the secondary antipsychotic has to be equal to or less than the equivalent dose of the primary antipsychotic and the sum of the primary and secondary antipsychotics must be ≤ 6 mg of risperidone equivalents.
9. Has an identified informant, considered reliable by the Investigator, (or designee), to provide support to the patient to help ensure compliance with study treatment, study visits and protocol procedures. The informant should know the patient for at least 3 months, see the patient outside of the clinical context on a weekly basis, and should be able to provide information on the patient helpful for completing study rating scales. The informant should be available for telephone interviews throughout the study and attend study visits when possible.
10. Fluent in English.
11. A body mass index (BMI) between 18 and 38 kg/m^2 inclusive.
12. For women of childbearing potential: Use contraceptive methods (hormonal or non-hormonal) that result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of study drug.

    Note: A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing

intrauterine devices, and copper intrauterine devices.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Pregnant or lactating.
2. Current DSM-5 diagnosis other than schizophrenia including bipolar disorder, schizoaffective disorder and major depressive disorder (MDD).
3. Clinically significant metabolic, hepatic, hematological, pulmonary, cardiovascular, gastrointestinal or urological disorder.
4. Any history of diagnosed seizure disorder.
5. Clinically significant neurological illness or significant head trauma that affects cognitive function, in the judgment of the Principal Investigator (PI).
6. FSIQ ≤ 65~~<70~~ on the Wechsler Abbreviated Scale of Intelligence (WASI–II) at screening.
7. Any clinically relevant ECG abnormalities at screening, including an average triplicate QTcF above 450 msec.
8. Clinically significant abnormal vital signs or laboratory test results at screening.

   Specifically, ~~F~~*f*or the clinical chemistry parameters:

   - the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) *exceeding* 2 *fold* the upper limit of normal (ULN) ***in combination with*** the total bilirubin > ULN with the exception of Gilbert syndrome~~;~~
   - serum creatinine exceed*ing* 1.5-fold ULN.
9. Positive result at screening for hepatitis B (HBV), hepatitis C (HCV, untreated), or human immunodeficiency virus (HIV)-1 and -2. HCV patients who have been successfully treated and who test negative for HCV RNA, may be considered eligible for entry into the study. *See Section 4.6.1.6, viral serology, laboratory assessments.*
10. Concomitant use of prohibited medications (see Section 4.5.2).
11. Moderate to severe substance use disorder (other than nicotine or caffeine), as defined by the DSM-5, within the last 12 months.
12. Confirmed positive test for alcohol or drugs of abuse at screening or at baseline.
13. Failure to detect blood concentrations of the prescribed antipsychotic medication. *If* no commercial test is available for recently approved antipsychotics, *the* decision will be taken on a case by case basis between the Investigator and the Roche TML (or designee).
14. Subjects with a history of poor compliance in the last 2 years.
15. Subjects who have experienced a change in their living situation in the last 3 months which would preclude the availability of a reliable informant.
16. Suicide attempt within one year or currently at risk of suicide in the opinion of the Investigator.
17. Receipt of an investigational drug within 3 months prior to screening.
18. Any medical condition or other factors, as judged by the Investigator, which may interfere with the subjects' participation or his/her ability to participate in this study.
19. A planned hospitalization during the time of the study (i.e., for elective surgery. Note that the one-week in-patient stay for the first approximately 40 patients is not

exclusionary).

LENGTH OF STUDY

The total duration of the study for each enrolled subject will be up to 34 weeks (from screening through completion of the last the last follow-up visit): 5-week Screening phase *which includes a placebo test phase*, 24-week treatment period *with study drug*, and 4-week follow-up period.

END OF STUDY

The end of the study is defined as the date when the Last Patient, Last Observation (LPLO) occurs. LPLO is expected to occur approximately 28 weeks after enrollment of the last study subject.

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence, nature and severity of adverse events (AEs).
- Incidence, nature and severity of treatment discontinuations due to AEs.
- Change from baseline in Systolic (SBP) and diastolic blood pressure (DBP) and pulse rate (PR).
- The following ECG parameters will be obtained: HR, PQ (PR), QRS, QT, RR and QTcF along with information on T- and U-waves.
- Changes in ECG parameters as compared to baseline ECG.
- Incidence of clinically significant ECG abnormalities.
- Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results:
    - Hematology: Hemoglobin, hematocrit, erythrocytes (RBC), platelets, leukocytes (WBC) differential (counts): neutrophils, eosinophils, lymphocytes, monocytes, basophils.
        - Blood chemistry: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and conjugated bilirubin, alkaline phosphatase (ALP), albumin, creatinine, urea, total protein, total cholesterol, triglycerides, sodium, chloride, calcium, phosphate, potassium, glucose.
    - Urinalysis: protein, blood, glucose, leukocytes, nitrites and pH.
- The Extrapyramidal Symptom Rating Scale – abbreviated version (ESRS-A).
- The PANSS items comprising the positive symptoms and hostility/excitement factors (for in-patients only).
- Suicidality assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).
- The Nurse's Observation Scale for In-patient Evaluation - 30 items (NOSIE-30) (for in-patients only).

PHARMACOKINETIC OUTCOME MEASURES

The PK outcome measures are:

- Population and individual primary PK parameters estimation (e.g., apparent clearances and volumes) and the influence of various covariates on these parameters.
- Secondary PK parameters (e.g., area under the curve [AUC] and C_{max}) derived from the individual post-hoc predictions.

EFFICACY OUTCOME MEASURES

The efficacy outcomes measures for this study are:

- MCCB neurocognitive composite score.

- WMS IV-PAL score.
- WMS IV-LM score.
- Trail Making test part B (TMT-B) and part A (TMT-A).
- Personal and Social Performance (PSP) scale.
- Schizophrenia Cognition Rating Scale (SCoRS).
- Clinical global impression – severity (CGI-S).
- Clinical global impression – improvement (CGI-I).

PATIENT–REPORTED OUTCOME MEASURES

The patient-reported outcome measures for this study are as follows:

- Schizophrenia Quality of Life Scale (SQLS).
- Smartphone-based Likert scales evaluating mood, sleep, subjective well-being and cognitive functioning and treatment expectancy.

EXPLORATORY OUTCOME MEASURES

The exploratory outcome measures for this study include but are not limited to the following:

- Positive and Negative Syndrome Scale (PANSS).
- Brief Negative Symptom Scale (BNSS).
- The Category Fluency test of the MCCB (semantic priming).
- The Hopkins Verbal Learning Test of the MCCB (primacy and recency effects).
- Virtual Reality Functional Capacity Assessment Tool (VRFCAT).
- University of Miami Computerized Functional Assessment System (CFAS).
- The work readiness questionnaire (WoRQ).

BIOMARKER/GENOTYPING SAMPLE COLLECTION

Two whole blood samples will be collected for (1) Research Biosample Repository (RBR) long-term storage for e.g., future genotyping for consortia contributions, and (2) DNA extraction for genotyping those genes associated with cognition, brain plasticity, and gamma-aminobutyric acid (GABA)- and glutamatergic functioning, as well as the complement C4 copy number variants (CNVs).

INVESTIGATIONAL MEDICINAL PRODUCT(S)

Test product

The study drug basmisanil will be provided in an immediate-release granule formulation packaged in sachets (“stick-packs”) containing 40 mg or 120 mg of basmisanil per sachet; two sachets to be administered orally twice daily.

Placebo

The placebo will be provided in a matching formulation, to be administered according to the same schedule as the study drug.

PROCEDURES

Informed consent will be obtained prior to any study-specific procedures. Following eligibility at screening *(including Evaluation to Sign Consent [ESC]*) and confirmation at baseline, patients will be enrolled into the study. The assessments and examinations will be conducted as described in the Schedule of Assessments.

The first approximately 40 eligible patients will be enrolled in the study as in-patients and will remain under supervision in the hospital for the first week of dosing. During this period,

additional assessments will be conducted as described in the Schedule of Assessments.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary analysis population for all efficacy analyses will be based on the ITT population, which will include all randomized patients treated with study medication. The primary efficacy endpoint (change from baseline to Week 24 in MCCB neurocognitive composite score) will be analyzed using a mixed effect model for repeated measures (MMRM) with treatment, region, age group, sex, schizophrenia cognitive subtype, and visit as fixed effects, treatment-by-visit interaction term, and baseline value as the covariate. The model will include subject as a random effect, and incorporate an unstructured variance-covariance matrix. For each active dose arm tested at the final analysis, this model will be used to test the null hypothesis of no treatment difference between the placebo arm and the active arm at a 2-sided α-level of 0.1.

SAFETY ANALYSES

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

As appropriate, listings, summary tables and graphs will be provided for safety and tolerability assessments, including:

- Incidence of AEs (overall, by intensity and by relationship to study medication).
- Incidence of SAEs.
- Incidence of laboratory abnormalities (including hematology, clinical chemistry, and urinalysis parameters).
- Incidence of blood pressure (BP) abnormalities.
- Incidence of ECG abnormalities as well ECG changes as compared to baseline measurements.
- Changes in the PANSS as compared to baseline.
- NOSIE-30 as compared to baseline.
- Changes in C-SSRS as compared to baseline.

Safety data will be summarized using descriptive statistics using the safety analysis population, which will include all patients treated.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Individual and mean plasma concentrations at each sampling time-point will be presented by listings and descriptive summary statistics, including means, medians, geometric means, ranges, standard deviations, and coefficients of variation. Individual and mean plasma concentration versus time data will be plotted on semi-logarithmic scales.

Graphical exploration of the relationship between basmisanil (and M1 and other metabolites, if relevant), exposure and outcome measures as well as safety parameters will be performed. If indicated by such exploration, more formal analyses of PK to pharmacodynamics (PD) parameters of interest may be undertaken.

PATIENT-REPORTED OUTCOME ANALYSES

The patient reported outcomes are:

- Change from baseline on the patient-reported health-related quality of life scale (SQLS)**.**
- Change in subjective mood, sleep and subjective well-being and cognitive functioning ratings.

These endpoints will be analyzed using an MMRM model similar to that described for the primary endpoint, and summarized using descriptive statistics.

EXPLORATORY ANALYSES

The exploratory analyses will include:

- Mean change from baseline in the PANSS factor and total scores.
- Mean change from baseline in the BNSS subscales and total scores.
- Mean change from baseline in % of patients rated as "ready to work" on the WoRQ.
- Mean change from baseline in the VRFCAT score.
- Mean change from baseline in the CFAS score.
- Semantic priming analysis of verbal fluency, as described in Section 4.6.1.9.
- Primacy region analysis of episodic verbal learning and recall. Percentage recall from the primacy relative to the recency region will be calculated for each learning trial and for long-delay free recall.
- Analysis of genetic PRS and complement C4 CNV as described in Section 3.2.3, and the 15q11-q13 chromosomal region including the GABRs GABRB3, GABRB5 and GABRG3 genes.

These endpoints will be analyzed using an MMRM or ANCOVA model as appropriate, and summarized using descriptive statistics.

SAMPLE SIZE JUSTIFICATION

A sample size of 50 patients per arm provides 80% power to detect a treatment effect size of 0.5, at a 2-sided α-level of 0.1, for the pairwise comparison of each active dose arm to placebo. No adjustments for multiple comparisons will be incorporated into the analysis. Incorporating an assumed premature rate of 35%, a study sample size of 231 (77 patients per arm) will be used. The sample size may be increased if the actual premature rate is higher than expected.

Interim Analyses

An interim analysis will be conducted when approximately 30 patients per arm have completed the first 12 weeks of treatment. The analysis will be conducted by the efficacy IMC.

This analysis will focus on the change from baseline to Week 12 in MCCB neurocognitive composite score, which will be analyzed using an MMRM model which will be similar to that described for the primary analysis (including all stratification factors although this may not be possible depending on the actual cell size). The pairwise comparison of each active dose to placebo will be evaluated using the estimated effect size based on the least-squares mean (LSM) estimates from the MMRM models. For each dose arm, the decision whether to continue or drop the arm for the remainder of the study will be based on the *conditional* probability that the true treatment effect size for that arm is ≥ 0.35. If the calculated *conditional* probability is less than 20% that the true treatment effect size can reach this threshold for one of the two doses, then that dose arm may be discontinued. If this *conditional* probability is less than 20% for both dose arms, then the study may be discontinued for futility.

In case the calculated *conditional* probability that the true treatment effect size can reach the threshold of effect size > 0.35 is more than 20% for both treatment arms, one treatment arm may still be discontinued.

Further analysis details on the interim analysis will be documented in a separate Efficacy IMC Agreement Document prior to the conduct of the interim analysis.

LIST OF PROHIBITED MEDICATIONS

Prohibited therapies should not be administered during the time period from at least 5 days (or 5 half-lives, whichever is longer) prior to initiation of study treatment until the end of the follow-up period, unless otherwise specified.

GABAergic medications

There is the potential for interactions to occur between basmisanil and other compounds whose effects are mediated via $GABA_A$ receptors. Because of the potential for basmisanil to compromise effectiveness of the GABAergic medications (i.e., a higher dose may be required to achieve the desired effect) and vice versa, use of the agents listed below will not be permitted during the study, from screening to the end of the follow-up period:

- General use of GABAA Positive Allosteric Modulators (GABAA PAMs; e.g., barbiturates, benzodiazepines and benzodiazepine-related drugs). The use of these agents will be permitted for insomnia and anxiety/agitation with the restrictions described below:
- For insomnia: zolpidem up 10 mg/d.
- For anxiety/agitation: Lorazepam PRN usage permitted with a maximum of 2 mg/week.
- $GABA_A$ PAMs must not be used within 12 hours of any cognitive assessment. At every visit when cognitive testing is scheduled as per Appendix 1, benzodiazepine intake will be evaluated by asking the patient about his consumption in the past week, and benzodiazepine blood levels will be measured (see Section 4.6.1.6).
- GABA transaminase inhibitors (e.g., phenelzine, valproic acid and vigabatrin).
- GABA reuptake inhibitors (e.g., tiagabine).
- Other anxiolytics, hypnotics and sedatives (e.g., chloral hydrate, ethchlorvynol, meprobamate, methaqualone, paraldehyde). Low doses of trazodone or mirtazapine at night as 'sleep aid pill', or hydroxyzine, are allowed.
- Anesthetics (e.g., chloroform, desflurane, etomidate, ketamine, propofol).
- GABAA antagonists (e.g., flumazenil); Note: emergency use will require the subject to withdraw from the study.
- GABA dietary supplements.
- Other medications that could have a pharmacodynamic interaction with basmisanil: gabapentin, pregabalin, lamotrigine, topiramate.

Modulators of CYP3A4 Activity

Basmisanil is predominantly cleared by metabolism via CYP3A4 and concomitant medications which significantly alter CYP3A4 activity will affect the pharmacokinetics of basmisanil. Medications which are prohibited include:

- Moderate or strong inhibitors of CYP3A4 (e.g., itraconazole, erythromycin, fluconazole, nefazodone, ritonavir, verapamil, grapefruit or grapefruit juice).
- Inducers of CYP3A4 (e.g., rifampicin, carbamazepine, pioglitazone, rifampin, modafinil, systemic glucocorticoids, St John's Wort.
    - For Inducers of CYP3A4, the washout window rule is to stop treatment 30 days or 5 half-lives prior to study drug administration, whichever is longer.

In case concomitant medications are needed that are moderate or strong CYP3A4 inhibitors, the patient should be withdrawn from the study.

Methods of administration which do not produce appreciable systemic drug exposure (e.g., topical administration for skin conditions) are permitted.

[redacted]

Diphenhydramine

Diphenhydramine is not permitted because of potential cardiac effects.

Dofetilide

Dofetilide use is not permitted because of the potential for interaction between basmisanil and renally-cleared cationic drugs, as well as the very narrow therapeutic window of dofetilide.

Anticholinergic medications

Anticholinergic (e.g. benztropine, biperiden, or trihexyphenidyl) are prohibited during the trial due to potential negative impact on cognition and the potential to interfere with the study primary endpoint. Anticholinergics prescribed as prophylaxis treatment for extrapyramidal symptoms need to be washed-out prior to enrollment. If deemed necessary by the PI, beta blockers (e.g. propranolol) can be prescribed instead.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BACS	Brief assessment of cognition in schizophrenia
BID	*Bis in die* (twice daily)
BMI	Body mass index
BNSS	Brief negative symptom scale
BP	Blood pressure
BUN	Blood urea nitrogen
CFAS	Computerized functional assessment system
CGI-I	Clinical global impression – improvement
CGI-S	Clinical global impression – severity
CIAS	Cognitive impairment associated with schizophrenia
CL	Clearance
CNS	Central nervous system
CNV	Copy number variant
CRO	Contract research organization
C-SSRS	Columbia suicide severity rating scale
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
DSUR	Development Safety Update Report
EC	Ethics committee
ECG	Electrocardiograms
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EEG	Electroencephalogram
ePRO	Electronic patient-reported outcome

EPS	Extrapyramidal symptoms
ESC	*Evaluation to sign consent*
ESF	Eligibility screening form
ESRS-A	Extrapyramidal symptom rating scale – abbreviated version
EU	European Union
FDA	Food and Drug Administration
FSIQ	Full scale IQ scores
GABA	Gamma-aminobutyric acid
GABR	$GABA_A$ receptor subunit genes
GFR	Glomerular filtration rate
GLP	Good laboratory practice
GWAS	Genome-wide association studies
HBsAG	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HCV	Hepatitis C virus
HDL	High-density lipoproteins
hERG	Human ether-a-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IC_{50}	Concentration values causing 50% inhibition
ICH	International Conference on Harmonisation
ICP	Idiopathic canine polyarteritis
IEC	Independent Ethics Committee
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational new drug (application)
INR	International normalized ratio
IQ	Intelligence quotient
IRB	Institutional review board
IUD	Intrauterine device
IxRS	Interactive (voice/web) response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LPLO	Last patient, last observation
LSM	Least-squares mean
LTP	Long-term potentiation
MAD	Multiple-ascending doses

MATRICS	Measurement and treatment research to improve cognition in schizophrenia
MCCB	MATRICS consensus cognitive battery
MDD	Major depressive disorder
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed effect model for repeated measures
MTD	Maximal tolerated dose
MWM	Morris water maze
NAM	Negative allosteric modulator
NMDA	N-methyl-D-aspartate
NMDAR	NMDA receptor
NOAEL	No-observed-adverse-effect level
NOR	Novel object recognition
NOSIE	Nurses' observation scale for in-patient evaluation
OTC	Over-the-counter
PAMs	Positive allosteric modulators
PANSS	Positive and negative syndrome scale
PBPK	Physiologically-based pharmacokinetic
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PR	Pulse rate
PRI	Perceptual reasoning index
PRN	*Pro re nata*, meaning 'as needed'
PRO	Patient-reported outcome
PRS	Polygenic risk score
PSP	Personal and social performance scale
PSQI	Pittsburgh Sleep Quality Index
PT	Prothrombin test
PTZ	Pentylenetetrazol
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia correction factor
QTcV	QT corrected for heart rate using van de Water's formula
RBC	Red blood cell
RBR	Research biosample repository

RNA	Ribonucleic acid
RR	RR interval
SAD	Single-ascending dose
SAE	Serious adverse event
SAR	Serious adverse reaction
SBP	Systolic blood pressure
SCoRS	Schizophrenia cognition rating scale
SI	*Système International d'Unités*
SNP	Single nucleotide polymorphism
SoA	Schedule of Assessments
SOFAS	Social and Occupational Functioning Assessment Scale
SPA	Statistical programmer
SQLS	Schizophrenia quality of life scale
SUSAR	Suspected unexpected serious adverse reactions
TMT	Trail making test
ULN	Upper limit of normal
US	United States
V	Volume
VCI	Verbal comprehension index
VRFCAT	Virtual reality functional capacity assessment tool
WASI-II	Wechsler abbreviated scale of intelligence
WBC	White blood cell
WGS	Whole genome sequencing
WMS IV-LM	Wechsler memory scale - Fourth edition, Logical memory test
WMS IV-PAL	Wechsler memory scale - Fourth edition, Verbal paired associates
WoRQ	Work readiness questionnaire

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON DISEASE

Schizophrenia is a heritable condition characterized by psychotic, so-called positive symptoms, negative symptoms and cognitive deficits. Both negative symptoms and cognitive deficits are major determinants for functional outcome (Green 2000). Cognitive deficits are often present before onset of psychosis (Reichenberg et al 2010) and are not treated by antipsychotic drugs indicating that the dopaminergic abnormalities driving positive symptoms are not a factor underlying cognitive deficits (Keefe et al 1999, Minzenberg and Carter 2012). Therefore, there is a high need for effective treatments for cognitive deficits associated with schizophrenia. Key cognitive deficits in schizophrenia involve functions that are mediated by the hippocampus and prefrontal cortex such as learning, memory, executive functions and attention. Preclinical, imaging and recent human electrophysiological and functional imaging studies have demonstrated the interdependence of hippocampal and prefrontal abnormalities and alterations in hippocampal-prefrontal interactions in individuals with schizophrenia (Sigurdsson and Duvarci 2016).

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. Numerous studies have consistently shown cortical GABAergic inhibitory circuits to play a pivotal role in regulating brain plasticity both during development and in adulthood. In primates, the maturation of cortical GABAergic circuitry extends into late adolescence and early adulthood, and thus, coincides with the vulnerable period for schizophrenia onset. It has therefore been argued that the neuropathology of schizophrenia may include abnormal post-natal development of the GABAergic systems and result in the emergence of symptoms during adolescence when the GABAergic system undergoes critical maturational changes (Lewis et al 2004). Indeed, dysfunction of GABA-mediated neurotransmission in schizophrenia is supported by post-mortem findings that included abnormalities in interneuron numbers, $GABA_A$ receptor binding activity on pyramidal neurons and GAD67 expression (Benes et al 2015). In addition, it has been postulated that these deficits converge on a common pathological mechanism that involves N-methyl-D-aspartate (NMDA) receptor hypofunction and oxidative stress (Hardingham and Do 2016). NMDA receptors are essential for several forms of synaptic plasticity and play a critical role in learning and memory (Paoletti et al 2013). One of the key models of the pathophysiology of schizophrenia in recent years has been the theory of NMDA receptor hypofunction – postulating that deficient signaling through this receptor underlies key deficits and symptoms of schizophrenia, including cognitive impairments (Coyle 2012).

1.2 BACKGROUND ON BASMISANIL

Basmisanil (RO5186582) is a novel negative allosteric modulator (NAM) of GABA type A ($GABA_A$) receptors which combines both binding and functional selectivity at the $GABA_A$ α5 subunit-containing receptors. At the time of writing, basmisanil is in clinical

development for the treatment of intellectual disability associated with Down syndrome (DS). Clinical development is also being initiated in stroke recovery and a Phase IIa study in stroke recovery patients is planned.

Among the different $GABA_A$ receptor subtypes, $GABA_A$ $\alpha5$ subunit-containing receptors are preferentially localized in the hippocampus and prefrontal cortex, key regions in the physiopathology of schizophrenia. This receptor subtype plays a key modulatory role in cognition (Collinson et al 2002, Crestani et al 2002). They are located at the base of dendritic spines of pyramidal cells and modulate excitatory glutamatergic input through the NMDA receptor (Möhler and Rudolph 2004). Thus, they modulate a key receptor involved in learning and memory which provides a mechanistic explanation on why $GABA_A$ $\alpha5$ NAMs improve cognition in mice (Dawson et al 2006, Martinez-Cue et al 2013), rats (Ballard et al 2009), non-human primates (Ballard et al 2009) and humans (Nutt et al 2007). As memory and learning are among the key functions deficient in schizophrenia, treatment with $GABA_A$ $\alpha5$ NAMs can be expected to ameliorate these deficits.

In addition, consistent with the modulation of NMDA signaling by $GABA_A$ $\alpha5$ receptor activity, $GABA_A$ $\alpha5$ NAMs have been shown in recent studies to improve cognitive impairment in preclinical models of NMDA receptor (NMDAR) dysfunction. Specifically, a $GABA_A$ $\alpha5$ NAM ameliorated deficits in the novel object recognition (NOR) test – a classical test of memory - and attentional set-shifting induced by subchronic and neonatal administration of phencyclidine in rats, respectively (Redrobe et al 2012). Moreover, other $GABA_A$ $\alpha5$ NAMs attenuated MK-801 induced deficits in an incremental repeated acquisition task (Povroznik et al 2014), and in the NOR and Morris-Water Maze (MWM) tasks (Stamenic et al 2015). Therefore, the strong evidence for a key role of $GABA_A$ $\alpha5$ receptors in cognitive functioning, particularly functions that depend on the integrity of hippocampal and prefrontal circuits, suggests that negative modulation of $GABA_A$ $\alpha5$ receptors by $GABA_A$ $\alpha5$ NAMs such as basmisanil may represent an effective treatment option for cognitive impairments associated with schizophrenia.

See the Basmisanil Investigator's Brochure for further details on non-clinical and clinical studies.

1.2.1 Previous Non-Clinical Studies

1.2.1.1 Non-Clinical Pharmacology

In vitro, basmisanil was shown to be a potent NAM at the $GABA_A$ $\alpha5\beta3\gamma2$ receptor subtype with both binding and functional selectivity. Basmisanil exhibited more than 90-fold binding selectivity for the human $GABA_A$ $\alpha5$ receptor subtype compared to $GABA_A$ $\alpha1$, $\alpha2$, $\alpha3$, $\alpha4$, and $\alpha6$ subunit containing receptors. In the Ts65Dn mouse model of Down syndrome which shows pronounced cognitive deficits, basmisanil rescued the deficit in Long-Term Potentiation (LTP) observed in hippocampal slices of these animals, demonstrating its ability to indirectly enhance NMDA receptor function.

In vivo, basmisanil exhibited cognition enhancing properties in two species in validated procedures that measured cognition in normal animals, as well as in Ts65Dn mice. In rats, basmisanil reversed scopolamine-induced impairment of associative learning in the fear-conditioning task and working memory impairment in the delayed-match-to-position task and diazepam-induced spatial learning impairment in the MWM. In monkeys, basmisanil improved executive function in the object retrieval task and improved short-term memory in the delayed-match-to-sample task. In Ts65Dn mice, basmisanil reversed the spatial learning deficit observed in the MWM after chronic treatment at receptor occupancy of 25% - 40%.

For further information, please refer to the Basmisanil Investigator's Brochure.

1.2.1.2 Non-Clinical Pharmacokinetics and Metabolism

[redacted]

Basmisanil is metabolized predominantly by cytochrome P450 (CYP)3A4 and to a lesser extent by CYP2C9 and CYP2D6. Overall, the rat and dog showed similar oxidative metabolic profiles to that of humans and were thus chosen as the relevant species for toxicity testing.

[redacted]

[redacted]

1.2.2 Previous Clinical Studies

At the time of writing, basmisanil has been investigated in 11 completed Phase 1 clinical studies in healthy adults (Studies BP25129, WP25366, WP28214, WP28978, JP29312, WP29393, WP29394, WP29402, and BP29784); one study enrolling both healthy adult subjects and adults with Down Syndrome (BP25611) and one study in young adults with Down syndrome (BP25543).

A total of 227 healthy subjects and 38 adults with Down syndrome participated in these 11 completed clinical studies in which 195 healthy volunteers and 28 adults with Down syndrome have been exposed to at least one dose of basmisanil.

At the time of writing, basmisanil is currently being tested in a Phase II study in adults and adolescents with Down syndrome (BP27832; “CLEMATIS”) and a second study in children with Down syndrome aged 6-11 years (WP27860).

1.2.2.1 Safety and Tolerability

The highest doses employed in the single-ascending dose (SAD) study (BP25129, 1250 mg) and in the MAD studies (WP25366, 1000 mg BID; BP25543, 370 mg BID) did not reach the maximum tolerated dose (MTD). Across clinical studies, no adverse event (AE) pattern has emerged that would be regarded as characteristic of basmisanil.

In the MAD study WP25366 and in the drug-drug interaction (DDI) study with itraconazole (WP29402), there was a signal for an initial, mild increase in heart rate and BP that became less apparent whilst dosing up to steady-state was continued. These cardiovascular observations were not reproduced in subjects with Down syndrome (BP25543); however, the data were too variable to exclude a possible cardiovascular effect.

Prolongation of mean QTcF intervals was observed in Study WP29402 in which basmisanil 240 mg BID was co-administered with itraconazole resulting in a 4- to 5-fold increase in basmisanil plasma concentrations. No relevant AE pattern of basmisanil emerged in this study. A mean increase in heart-rate corrected QT interval using Fridericia’s formula (QTcF) of 4.5 and 9.5 milliseconds (ms) was seen around the time to maximum plasma concentration (T_{max}) of basmisanil following 10 days of co-administration of basmisanil 120 mg BID and 240 mg BID, respectively, with itraconazole. In subjects with normal hepatic clearance of basmisanil (e.g., in the absence of moderate or strong CYP3A4 inhibitors or absence of impaired liver function), no relevant increase in QTc can be assumed.

Across clinical studies, increased serum creatinine concentrations were found with higher basmisanil doses. However, individual values typically remained within the standard reference range and changes were not judged to be clinically relevant. Furthermore, they were not associated with changes of other glomerular filtration rate (GFR) markers, i.e., iohexol clearance and cystatin C in serum. Thus, the elevations in serum creatinine are likely related to inhibitory effects of basmisanil on the tubular creatinine transporters as shown in vitro. Of note, the magnitude of the serum creatinine increase matches the fraction of creatinine clearance through tubular secretion and such increases returned to normal shortly after treatment stop.

Of note, non-selective $GABA_A$ $\alpha5$ NAMs may be associated with side-effects related to interaction with $GABA_A$ $\alpha1$, $\alpha2$, and $\alpha3$ receptors, such as convulsions, sleep problems or anxiety. In contrast, basmisanil is a highly selective $GABA_A$ $\alpha5$ NAM and previous clinical trials did not reveal a basmisanil-related alert for such side-effects. In particular, electroencephalogram (EEG) monitoring did not reveal treatment emergent epileptiform

abnormalities including at exposures higher than those produced with a 240 mg BID doing regimen (WP25366, WP29402).

In the currently ongoing clinical trials BP27832 ("CLEMATIS") and WP28760, no safety alerts for basmisanil have emerged. This includes preliminary analysis of safety data from Study BP27832 as of May 2016. From the 170 subjects enrolled, 112 subjects were randomized to one of the two active treatment arms, and 57 subjects were allocated to the high-dose arm, i.e., 240 mg BID for the 14-30-year old subjects and 160 mg BID for the 12-13-year old subjects. A total of 156 subjects completed the entire 6-month treatment period while 14 subjects were pre-maturely withdrawn, 4 of those due to an AE.

For more details, please see the Basmisanil Investigator's Brochure.

[redacted]

See the Basmisanil Investigator's Brochure for more information.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

Recent studies on the genetics of schizophrenia have established an important role for rare (less than 1% in frequency) and large (more than 100 kilobase) copy number variants (CNVs) in the etiology of this disorder (Malhotra & Sebat 2012). Among the susceptibility loci identified, the 15q11-13 duplication was found to confer high-risk for schizophrenia (Malhotra & Sebat 2012, Rees et al 2014). This is a complex locus that contains, amongst others, a cluster of three $GABA_A$ receptor subunit genes (GABR): GABRB3, GABRA5 and GABRG3 which encode $GABA_A$ receptor subunits $\beta 3$, $\alpha 5$, and $\gamma 3$, respectively. The duplication is believed to lead to an abnormal overexpression of the respective subunits. In addition, genetic variation across these particular GABR subunit genes has also been associated with schizophrenia risk (Huang et al 2014, Beneyto et al 2011) and the severity of psychotic symptoms (Sun et al 2012, Bergen et al 2009) providing additional support for an involvement of abnormalities in these GABA subunits in the pathophysiology of schizophrenia.

As detailed above, $GABA_A$ $\alpha 5$ subunit-containing receptors are preferentially localized in the hippocampus and prefrontal cortex - key regions implicated in the physiopathology of schizophrenia and in particular, in cognitive deficits associated with schizophrenia. They are expressed at the base of dendritic spines of pyramidal cells allowing them to modulate excitatory glutamatergic input through the NMDA receptor (Möhler and Rudolph 2004). This provides a mechanistic explanation on why $GABA_A$ $\alpha 5$ NAMs improve cognition in rodents (Dawson et al 2006, Martinez-Cue 2013, Ballard et al 2009), non-human primates (Ballard et al 2009) and humans (Nutt et al 2007).

As reviewed in more detail in Section 1.2, the assumed improvement of NMDA signaling by $GABA_A$ $\alpha 5$ NAMs can plausibly explain the amelioration of cognitive impairment in preclinical models of NMDAR dysfunction. Therefore, the strong evidence for a key role of $GABA_A$ $\alpha 5$ receptors in cognitive functioning, particularly functions that depend on the integrity of hippocampal and prefrontal circuits, suggests that negative modulation of $GABA_A$ $\alpha 5$ receptors by $GABA_A$ $\alpha 5$ NAMs such as basmisanil may represent an effective treatment option for cognitive impairments associated with schizophrenia.

1.3.2 Benefit-Risk Assessment

Overall, in all clinical studies, basmisanil has been found to be safe and well-tolerated at the doses used in this trial without relevant effects on laboratory parameters. A trend for longer QTcF intervals at concentrations higher than achieved with the dose selected for this study (240 mg BID per oral) was observed. However, no relevant QTcF prolongation can be assumed for concentrations generated with a 240 mg BID dosing regimen in subjects with normal hepatic clearance of basmisanil (e.g., in the absence of moderate or strong CYP3A4 inhibitors or absence of impaired liver function). Patients with schizophrenia may be receiving atypical antipsychotics which may prolong QTc although the magnitude among antipsychotic drugs varies. While it is not assumed that basmisanil

will act synergistically with such antipsychotics on QTc, QTc interval will be monitored at the initiation of basmisanil treatment to address this risk.

Results obtained in preclinical models of schizophrenia have led to the hypothesis that positive rather than negative modulators of the $GABA_A$ $\alpha5$ receptor could be beneficial for control of positive symptoms of schizophrenia (Lodge and Grace 2011). Thus, a theoretical risk for $GABA_A$ $\alpha5$ NAMs to worsen psychotic symptoms could be inferred. However, when basmisanil was tested in clinical trials, even at high doses, no pro-psychotic liability emerged from AE reporting. Initiation of basmisanil treatment during an in-patient stay allows the management and evaluation of this theoretical and small risk.

Overall, the risk to patients with schizophrenia treated with basmisanil is considered small.

As outlined above, the unmet medical need for effective treatment for cognitive impairment associated with schizophrenia (CIAS) is enormous. Given the potential of basmisanil to significantly improve cognitive deficits in schizophrenia, the potential benefit to future patients, including those participating in this trial, would be significant. Thus, overall, the benefits outweigh the risks associated with basmisanil treatment.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is:

- To investigate the efficacy of 24 weeks of basmisanil treatment on cognitive function as measured by the MATRICS consensus cognitive battery (MCCB) neurocognitive composite score, in stable patients with CIAS treated with antipsychotics.

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

To evaluate the effect of 24 weeks of treatment with basmisanil in stable patients with CIAS treated with antipsychotics on the following:

- Individual cognitive domains of the MCCB, namely attention, speed of processing, reasoning, working memory, visual learning, verbal learning and social cognition.
- Additional specific hippocampal and prefrontal-dependent cognitive tasks and processes (as measured by the Trail making test [TMT]-B, Wechsler memory scale - Fourth edition, verbal paired associates [WMS IV-PAL] and Wechsler memory scale - Fourth edition, logical memory test [WMS IV-LM]).
- Functional capacity and performance (as measured by the Personal and Social Performance scale [PSP] and Schizophrenia Cognition Rating Scale [SCoRS]).

- To evaluate the safety and tolerability of 24 weeks of basmisanil treatment in patients with CIAS treated with antipsychotics.
- To characterize the steady-state pharmacokinetics (PK) of basmisanil and its metabolites, if appropriate, in stable patients with CIAS treated with antipsychotics using population PK modelling methods.

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To explore the effect of 24 weeks of treatment with basmisanil on semantic priming (measured in the category fluency test of the MCCB) and primacy/recency effects (measured in the Hopkins verbal learning test of the MCCB), two experimental measures of hippocampal-dependent cognitive processes.
- To determine whether the patients' genetic profile predicts effects of treatment with basmisanil on cognitive functions.
- To evaluate the effect of 24 weeks of treatment with basmisanil on self-reported mood, sleep, subjective well-being and cognitive functioning (smartphone-based assessments).
- To evaluate the effect of 24 weeks of treatment with basmisanil on functional capacity assessed by novel computerized measures and "work readiness".
- To evaluate the effect of 24 weeks of treatment with basmisanil on symptoms of schizophrenia including positive and negative symptoms.
- To evaluate the effect of 24 weeks of treatment with basmisanil on quality of life.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase IIb study, to evaluate the effects of 24 weeks of basmisanil treatment on CIAS in stable patients treated with antipsychotics.

The final analysis will investigate the PK, safety and tolerability, and efficacy of 24 weeks of basmisanil treatment on cognition and functioning.

3.1.1 Overview of Study Design

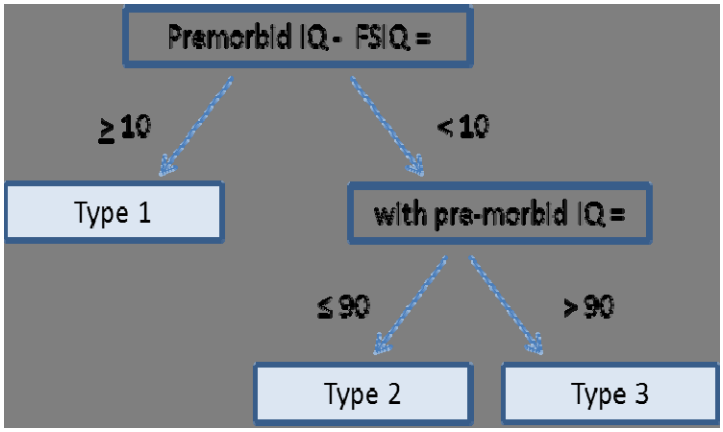
Two doses of basmisanil (240 mg, 80 mg) will be tested against placebo. Approximately 231 patients will be randomized to one of three treatment arms, in a 1:1:1 ratio:

- Arm 1: 240 mg BID (may be lowered to 120 mg BID upon Safety Internal Monitoring Committee [IMC] decision, see Section 3.1.3).
- Arm 2: 80 mg BID.
- Arm 3: Placebo BID.

The sample size may be increased if the actual premature withdrawal rate is higher than expected.

Randomization will be stratified based on age, sex and “schizophrenia cognitive subtype”. The stratification threshold for age will be ≤ 35 years and > 35 years. The “schizophrenia cognitive subtype” will be determined at screening based on the difference between the pre-morbid intelligence quotient (IQ), estimated by the wide range assessment test (WRAT)-4 reading test standard score, and current full scale IQ scores (FSIQ), estimated by the Wechsler Abbreviated Scale of Intelligence – second edition (WASI-II) as shown on Figure 1 .

Figure 1 Determination of the Schizophrenia Cognitive Subtype at Screening



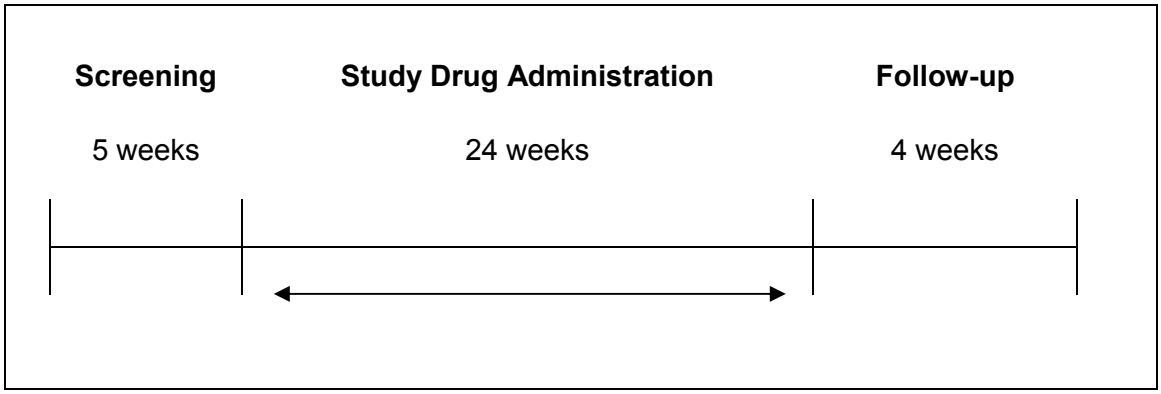
The study will be divided into 3 phases (Figure 2):

- A screening phase of approximately 5 weeks *which includes Baseline 1 and Baseline 2 visits.*
- A double-blind treatment phase *with study drug* of approximately 24 weeks.
- A follow-up phase of approximately 4 weeks after treatment discontinuation.

Efficacy, safety, and PK assessments will be conducted throughout the study, as detailed in the Schedule of Assessments (Appendix 1).

Patients will be treated until the end of the study treatment period, unacceptable toxicities, or withdrawal of consent.

Figure 2 Study Design



The total duration of the study for each enrolled subject will be up to 34 weeks (from screening through completion of the last the last follow-up visit): 5-week Screening phase *which includes a placebo test-phase*, 24-week treatment period *with study drug*, and 4-week follow-up period.

As detailed in Section 1.3.2, a small theoretical risk may exist for basmisanil to worsen psychotic symptoms. For this reason, approximately the first 40 patients enrolled will be in-patients for the first week of treatment, and their safety and mental state will be closely monitored. Assessments to be performed during the in-patient stay are detailed in the Schedule of Assessments (Appendix 1), under the column "in-patients only". Patients will be discharged on an individual basis at the Principal Investigator's (PI's) discretion, after a minimum of 7 days of treatment. The safety IMC will decide when newly enrolled patients can be started on study medication on an outpatient basis (see Section 3.1.3 for more details on the safety IMC).

3.1.2 Stopping Rules

Pre-set stopping rules for individual study subjects are defined as follows:

- One of the following QTcF findings:
  - A QTcF value exceeding CTCAE ≥Grade 2 or >480 msec (when confirmed in repeat measurement within 30 minutes),

OR

  - A QTcF value exceeding a change from baseline of 60 msec (when confirmed in repeat measurement within 30 minutes).

    If the QTcF does not normalize after discontinuation of the study drug and a washout period of 1 week, the patient should receive appropriate emergent treatment and be referred to a cardiologist for evaluation.
- Any subject suspected of having seizure activity during the study, must receive appropriate emergent treatment, the study drug must be stopped, and the patient must be referred to a neurologist for evaluation (An episode of seizure not resolving within 3 minutes should be reported as an SAE).

- Subjects with any elevated alanine aminotransferase (ALT)/elevated aspartate aminotransferase (AST) of $>3\times$ upper limit of normal (ULN), and associated with an increase in bilirubin ($\geq 2\times$ ULN) (i.e., a suspected "Hy's law" indicating risk of severe/serious liver impairment) in the absence of a different explanation. Such abnormalities should be followed by repeat testing within 48 to 72 hours and repeated two to three times weekly based on the patient's clinical state. An evaluation by a hepatologist may be required if the abnormalities do not stabilize. All subjects with possible drug-induced liver injury should be followed until abnormalities return to normal even if the study drug has been discontinued.
- Subjects who have creatinine increases above $1.5\times$ ULN that are confirmed on repeat testing within approximately 3 days.

3.1.3 Internal Monitoring Committees (IMCs)

This study will utilize a safety IMC and an efficacy IMC. All data analysis for the safety IMC and efficacy IMC reviews will be performed by the study statistician and the study statistical programming team.

3.1.3.1 Safety IMC

A Roche safety IMC will have safety oversight responsibility for the in-patient treatment part of this study. This safety IMC will consist of:

- A clinical scientist, separate from the project team and who does not interact with the sites on a regular basis.
- A clinical safety physician separate from the project team and who does not interact with the sites on a regular basis.
- A clinical pharmacology leader who may be from the project team, but does not interact with the sites on a regular basis.
- The study statistician.

The safety IMC will review and evaluate the unblinded safety data AEs, ECG, vital signs, global clinical condition and changes in symptomatology (and PK results if available), after 10, 25 and approximately 40 patients have reached one week of in-patient treatment. At any of these reviews of the safety data, the safety IMC will decide if further in-patient monitoring is needed for the subsequent patients enrolled or whether the study can be safely conducted with out-patient visits. Screening and enrollment should not be stopped. Participants who had started the in-patient period will remain as in-patient to finish the 1-week period. After patient 40, newly randomized subjects will participate as in-patients until the Sponsor indicates that sites are clear to randomize subjects as outpatients.

The safety IMC will specifically assess the changes from baseline in the ECG parameters (HR, QRS, QTcF), looking for a dose-response effect among cohorts or a correlation with exposure.

The AE profile as well as any evidence of emerging or worsening psychotic or other symptoms gleaned from validated instruments implemented (such as the positive and negative syndrome scale [PANSS] or the Nurse's Observation Scale for In-patient Evaluation - 30 items Scale [NOSIE-30]) will be carefully examined across cohorts by the safety IMC.

The safety IMC will also review the concomitant anti-psychotic therapies for the enrolled patients looking for DDIs or safety concerns based on the AE profile, ECG parameters and vital signs.

In case of clinically significant safety findings in the 240 mg cohort including a report of a Serious Adverse Reaction (SAR) attributable to basmisanil, QTcF values above 480 msec or an increase of QTcF of $>$60 msec from baseline, suspected seizure activity, or significant worsening of the underlying schizophrenia, the safety IMC can advise to stop enrolling in this cohort and to discontinue the patients in the 240 mg BID cohort from the study. In this case, a new dose arm of 120 mg BID will be opened. Patients who would have been newly randomized to the highest dose (240 mg BID) would from then on be randomized to 120 mg BID treatment. The safety IMC can reinstitute the in-patient monitoring for patients randomized to 120 mg BID with reviews after 10, 25 and 40 patients to ensure the safety of the 120 mg BID dose in the schizophrenia patient population treated on an out-patient basis. Additional details may be found in the Safety IMC Agreement Document.

All safety data obtained during outpatient treatment in this study will be reviewed throughout the study by the Sponsor in a treatment-blinded manner.

3.1.3.2 Efficacy IMC

Once approximately 90 patients have completed at least 12 weeks of treatment, an efficacy IMC (consisting of the members of the safety IMC along with the study translational medicine leader, a senior Roche clinical representative independent from the study team, a pharmacometrician, and others who will be involved in the decision-making process as needed) will conduct an interim analysis for futility on the primary endpoint of the study. The committee will review and evaluate the data unblinded at the group level (including safety data and PK results if available), and the decision will be taken to either continue the study unchanged, to stop one arm or to end the study. Descriptions of the conduct of the analysis, including pre-defined success criteria for the efficacy interim analysis, are summarized in Section 6.10 and will be described in further detail in a separate Efficacy IMC Agreement Document.

3.1.4 End of Study

The end of the study is defined as the date when the Last Patient, Last Observation (LPLO) occurs. LPLO is expected to occur approximately 28 weeks after enrolment of the last patient.

3.2 RATIONALE FOR STUDY DESIGN

This Phase IIb study is designed to provide initial safety and efficacy information of two doses of basmisanil against placebo, for the treatment of CIAS. The study is powered to detect an effect size of approximately 0.5.

As the time-course of potential cognitive effects is unknown and may not follow the known trajectory of symptomatic improvement, a study duration of six months was chosen as it is assumed that six months will provide enough time for any potential cognitive and functional effects to emerge.

3.2.1 Rationale for Dosage Selection

[redacted] These doses thus differentiate from one other and ensure that biologically relevant occupancy ranges are fully covered.

In addition, in a recently completed study (BP27832; “CLEMATIS”) for the treatment of intellectual disability associated with Down syndrome, a dose of 240 mg BID for up to 6 months in adults and adolescents was safe and well-tolerated.

3.2.2 Rationale for Study Population

This study will enroll stable male and female schizophrenic patients aged between 18 and 50 years, who have been on stable antipsychotic treatment for at least 3 months.

Cognitive impairment is a prominent feature of schizophrenia, with more than 80% of patients exhibiting deficits. The pattern of cognitive deficits associated with schizophrenia does not significantly differ between males and females. Both sexes are hence eligible for this study.

Multiple lines of evidence suggest that neuroplasticity and the capacity to learn are a function of age, which decrease in later adulthood. It is therefore hypothesized that the potential cognition-enhancing effects of basmisanil may be more readily detected in younger adults. As cognitive remediation therapies in the schizophrenic population have been shown to be most effective before the age of 50 years, the upper age limit of 50 years has been selected for this study.

3.2.3 Rationale for Biomarker Assessments

An individual’s genetic profile may predict response to $GABA_A$ $\alpha5$ NAM treatment, providing the opportunity to better understand the pathophysiology of CIAS and to develop a treatment response stratifier. Specifically, single nucleotide polymorphisms (SNPs) have been identified which are both associated with an increased risk for schizophrenia (Purcell et al 2009) as well as enhanced plasticity, GABA- or glutamatergic functioning, and cognitive functioning (Ripke et al 2014), and in non-clinical populations, SNPs which are associated with enhanced hippocampal-

dependent episodic memory functioning (Debette et al 2015) and general cognitive functioning (Davies et al 2015, 2016). The genetic profile corresponding to these SNPs can be quantified with a polygenic risk score (PRS), which weighs each SNP's allelic frequency with the respective genome-wide association studies (GWAS) odds ratio. Additionally, CNV of complement system C4A and C4B short and long forms have also been associated with an increased risk for schizophrenia and decreased hippocampal-dependent cognitive functioning (Sekar et al 2016). This study will therefore collect blood for analyses with standard SNP arrays and digital droplet polymerase chain reaction to determine whether the PRS and C4 CNVs, respectively, predict treatment response (i.e., change in MCCB neurocognitive composite score and other outcome measures) to basmisanil.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature and severity of AEs.
- Incidence, nature and severity of treatment discontinuations due to AEs.
- Change from baseline in Systolic (SBP) and diastolic blood pressure (DBP) and pulse rate (PR).
- The following ECG parameters will be obtained: HR, PQ (PR), QRS, QT, RR and QTcF along with information on T- and U-waves.
- Changes in ECG parameters as compared to baseline ECG.
- Incidence of clinically significant ECG abnormalities.
- Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results:
- Hematology: Hemoglobin, hematocrit, erythrocytes (RBC), platelets, leukocytes (WBC) differential (counts): neutrophils, eosinophils, lymphocytes, monocytes, basophils.
- Blood chemistry: Aspartate aminotransferase (AST), ALT, total and conjugated bilirubin, ALP, albumin, creatinine, urea, total protein, total cholesterol, triglycerides, sodium, chloride, calcium, phosphate, potassium, glucose.
- Urinalysis: protein, blood, glucose, leukocytes, nitrites and pH.
- The Extrapyramidal Symptom Rating Scale – abbreviated version (ESRS-A).
- The PANSS items comprising the positive symptoms and hostility/excitement factors (for in-patients only).
- Suicidality assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).
- The Nurse's Observation Scale for In-patient Evaluation - 30 items (NOSIE-30) (for in-patients only).

3.3.2 Pharmacokinetic (PK) Outcome Measures

The PK outcome measures are:

- Population and individual primary PK parameters estimation (e.g., apparent clearances and volumes) and the influence of various covariates on these parameters.
- Secondary PK parameters (e.g., AUC and C_{max}) derived from the individual post-hoc predictions.

3.3.3 Efficacy Outcome Measures

The efficacy outcome measures for this study are:

- MCCB neurocognitive composite score.
- WMS IV-PAL score.
- WMS IV-LM score.
- TMT part B (TMT-B) and part A (TMT-A).
- PSP scale.
- SCoRS.
- Clinical global impression – severity (CGI-S).
- Clinical global impression – improvement (CGI-I).

3.3.4 Patient-Reported Outcome Measures

The patient-reported outcome measures for this study are as follows:

- Schizophrenia Quality of Life Scale (SQLS).
- Smartphone-based Likert scales evaluating mood, sleep, subjective well-being and cognitive functioning and treatment expectancy.

3.3.5 Exploratory Outcome Measures

The exploratory outcome measures for this study include but are not limited to the following:

- Positive and Negative Syndrome Scale (PANSS).
- Brief Negative Symptom Scale (BNSS).
- The Category Fluency test of the MCCB (semantic priming).
- The Hopkins Verbal Learning Test of the MCCB (primacy and recency effects).
- Virtual Reality Functional Capacity Assessment Tool (VRFCAT).
- University of Miami Computerized Functional Assessment System (CFAS).
- The work readiness questionnaire (WoRQ).

4. MATERIALS AND METHODS

4.1 CENTER

This is a multi-center study to be conducted in the US. An additional site(s) may be included for back-up purposes and may be activated if needed.

Administrative and Contact Information, and the List of Investigators are provided separately.

4.2 STUDY POPULATION

The study population consists of male and female subjects with schizophrenia aged 18-50 years who are on stable antipsychotic therapy.

4.2.1 Recruitment Procedures

Patients will be identified for potential recruitment using pre-screening enrollment logs, Institutional Review Board (IRB)-approved newspaper/radio advertisements, mailing lists and referral networks.

4.2.2 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Male or female subjects aged between 18 and 50 years.
2. Able to participate and willing to give written informed consent.
3. *Able to understand key risk and benefits of the study as demonstrated by a score ≥ 10 on the Evaluation to Sign Consent (ESC) form.*
4. Able to perform study assessments and procedures and comply with the study protocol, including one week of hospitalization/in-patient stay.
5. Diagnosis of schizophrenia of any type utilizing the Mini International Neuropsychiatric Interview (MINI) and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) – direct clinical assessments, family informants and past medical records.
6. Evidence of stability of symptoms for 3 months at screening, i.e., without hospitalizations for schizophrenia or increase in level of psychiatric care due to worsening of symptoms of schizophrenia.
7. Schizophrenia clinical symptom severity defined by the following: Hallucinatory Behavior item score ≤ 5 and a Delusion item score ≤ 5 of the PANSS.
8. On a stable regimen of antipsychotic therapy for at least 3 months at screening and receiving no more than two antipsychotics. Antipsychotic regimen: Patients must be on a "primary" antipsychotic and may be on a secondary antipsychotic. The amount of the secondary antipsychotic has to be equal to or less than the equivalent dose of the primary antipsychotic and the sum of the primary and secondary antipsychotics must be ≤ 6 mg of risperidone equivalents (refer to Appendix 2 for conversion of antipsychotic doses to risperidone equivalents).

9. Has an identified informant, considered reliable by the Investigator (or designee) to provide support to the patient to help ensure compliance with study treatment, study visits and protocol procedures. The informant should know the patient for at least 3 months, see the patient outside of the clinical context on a weekly basis, and should be able to provide information on the patient helpful for completing study rating scales. The informant should be available for telephone interviews throughout the study and attend study visits when possible.
10. Fluent in English.
11. A body mass index (BMI) between 18 and 38 kg/m^2 inclusive.
12. For women of childbearing potential: Use contraceptive methods (hormonal or non-hormonal) that result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of study drug.

    Note: A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

4.2.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Pregnant or lactating.
2. Current DSM-5 diagnosis other than schizophrenia including bipolar disorder, schizoaffective disorder and major depressive disorder (MDD).
3. Clinically significant metabolic, hepatic, hematological, pulmonary, cardiovascular, gastrointestinal or urological disorder.
4. Any history of diagnosed seizure disorder.
5. Clinically significant neurological illness or significant head trauma that affects cognitive function, in the judgment of the PI.
6. FSIQ ≤ 65 on the Wechsler Abbreviated Scale of Intelligence (WASI–II) at screening.
7. Any clinically relevant ECG abnormalities at screening, including an average triplicate QTcF above 450 msec.
8. Clinically significant abnormal vital signs or laboratory test results at screening.

   Specifically, for the clinical chemistry parameters:

- the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) *exceeding* 2 *fold* the upper limit of normal (ULN) ***in combination with*** the total bilirubin > ULN with the exception of Gilbert syndrome
- serum creatinine exceed*ing* 1.5-fold ULN.

9. Positive result at screening for hepatitis B (HBV), hepatitis C (HCV, untreated), or human immunodeficiency virus (HIV)-1 and -2. HCV patients who have been successfully treated and who test negative for HCV RNA, may be considered eligible for entry into the study. *See Section 4.6.1.6 viral serology, laboratory assessments.*
10. Concomitant use of prohibited medications (see Section 4.5.2).
11. Moderate to severe substance use disorder (other than nicotine or caffeine), as defined by the DSM-5, within the last 12 months.
12. Confirmed positive test for alcohol or drugs of abuse at screening or at baseline.
13. Failure to detect blood concentrations of the prescribed antipsychotic medication. *If* no commercial test is available for recently approved antipsychotics, *the* decision will be taken on a case by case basis between the Investigator and the Roche TML (or designee).
14. Subjects with a history of poor compliance in the last 2 years.
15. Subjects who have experienced a change in their living situation in the last 3 months which would preclude the availability of a reliable informant (refer to Section 4.2.2).
16. Suicide attempt within one year or currently at risk of suicide in the opinion of the Investigator.
17. Receipt of an investigational drug within 3 months prior to screening.
18. Any medical condition or other factors, as judged by the Investigator, which may interfere with the subjects' participation or his/her ability to participate in this study.
19. A planned hospitalization during the time of the study (i.e., for elective surgery. Note: The one-week in-patient stay for the first approximately 40 patients is not exclusionary).

4.3 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Patients will be randomized to placebo, or one of the two active treatment doses (80 mg and 240 mg BID). Randomization will be stratified by sex, age, and cognitive subtype as described in Figure 1. The randomization numbers will be generated by the Sponsor or its designee. With the exceptions described below, the randomization list will not be available to the project team at Roche or to any personnel at the study centers.

The randomization list will be made available to the individual responsible for PK sample bioanalysis (and pharmacodynamics [PD] bioanalysis if appropriate). The list will also be provided to statisticians and programmers at Roche as needed to create unblinded data displays for the internal safety monitoring committee reviews and the efficacy interim analysis.

Emergency Unblinding:

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected serious adverse events (SAEs; see Section 5.1) that are considered by the Investigator to be related to study drug.

The PIs will receive a set of sealed treatment codes. If the identity of the test medication needs to be known in order to manage the patient's condition, the treatment code for that patient may be broken.

In the event of an emergency, the treatment code for an individual patient will be readily available to the Investigator and Sponsor through the interactive (voice/web) response system (IxRS).

All such occurrences should be documented in the study file. Treatment codes should not be broken except in emergency situations and, if possible, the responsible scientific leader should be contacted before the code is opened. At the final monitoring visit, the unused treatment codes will be counted and checked and a statement to the effect that all are intact (or not as the case may be) will be made by the monitor; this statement will be included or referred to in the final study report. All treatment codes will be returned to Roche.

Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data. Any unblinding, at the investigating site end, will be documented in the study report with date, reason for identifying the drug and the name(s) of all the person(s) who had to be unblinded.

4.4 STUDY TREATMENT

4.4.1 Formulation, Packaging, and Handling

The study drug basmisanil will be provided in an immediate-release granule formulation packaged in sachets ("stick-packs") containing 40 mg or 120 mg of basmisanil per sachet, two sachets to be administered orally twice daily. The placebo will be provided in a matching formulation, to be administered according to the same schedule as the study drug.

[redacted] 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. The packaging and labeling of the study medication will be in accordance with Roche standard and local regulations.

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.

For further details, see the Basmisanil Investigator's Brochure.

4.4.2 Dosage and Administration

The study medication is two stick-packs taken orally, twice daily (in the morning and in the evening within 30 minutes of a meal) over 24 weeks. Granules should be mixed with or sprinkled onto a small amount soft food (i.e., yogurt, apple sauce, or pudding) and all of the food consumed *or as an alternative, patients have the option of placing the granules directly into their mouth followed by swallowing with a glass of water. (Note: the granules must not be mixed with water before putting them into the mouth)*.

On Study Day 1, the first dose of medication will be administered in the hospital or at the clinic/study center once all pre-dose assessments have been conducted and eligibility has been confirmed. For all subsequent study visits, the morning dose will be taken at the study center. The last dose of medication will be the morning dose, administered at the clinic/study center at Week 24 visit.

Patients will be provided with a sufficient amount of medication to cover study treatment until the next site visit (including some overage). The qualified individual responsible for dispensing the study drug supply will prepare the correct medication supply required as instructed by IxRS and according to the randomization schedule. This individual will write the date dispensed and Patient Number on the study drug label and on the Drug Accountability Record. This individual will also record the study drug batch or lot number received by each subject during the study.

Guidelines for treatment interruption or discontinuation are provided in Section 3.1.2 and Section 4.7.1.

4.4.3 Medication Adherence and Engagement Systems

4.4.3.1 Medication adherence system

The patient's capacity to comply with taking twice daily study medication will be assessed during the screening period, between Baseline 1 and Baseline 2 visits. Patients will be asked to take placebo medication and to report each intake using *a medication adherence monitoring platform ("Platform")* provided on a smartphone. A compliance report will be made available to support the PI's assessment of the patient's capacity to comply with the study requirements (refer to Section 4.2.2, "Inclusion Criteria").

Patients will receive a medication reminder at a time within a pre-defined window to take their medication. Patients will follow a series of prescribed steps *using the front-facing camera* of the smartphone to confirm patient identity and medication to be taken. The

patient has to confirm ingestion of medication manually *as well as the chosen dosing method (i.e., soft food vs. direct intake) as soon as the platform has been updated to include this functionality*. In addition, built-in reminders and a communication system allows real-time intervention in case of non-compliance. Use of this Platform will in no way supersede or replace the physician and/or prescribed medication protocol. Because the Platform does not change the medication protocol, but rather encourages adherence, use of this Platform presents minimal risk to the patients.

After local determination by the Platform of proper medication administration, only data indicating whether or not the patient has properly taken the medication will be transferred to a secure centralized location. No video recordings or pictures identifying the patient will be stored on the smartphone nor transmitted to the server. The captured data is reviewable through a roles- and rules-restricted Health Insurance Portability and Accountability Act (HIPAA)-compliant system ensuring privacy of the information and only accessible to authorized personnel through two-way authentication.

Phone numbers of the patients will be collected and stored in an encrypted manner, allowing for direct communication to each patient from the system in an automated manner, or by study staff or other study monitoring personnel. Individuals not part of the study staff will not know the identity of study patients and will have no access to any medical or health records of the patients.

Patients who are found to regularly not take their medication will be contacted by study staff for retraining and motivational interventions.

4.4.3.2 Optional patient engagement system

Patients will also have the option to use a patient engagement application, referred to as a smartphone “App”.

The App is an optional service that patients can opt-in to use to remind them of activities/tasks relevant to study compliance, such as when to attend site visits. The App also provides supportive guides to help patients be aware of visit procedures, study information and instructions.

The App’s interactive features are intended to be a companion to the user during the course of a trial and include the following modules:

- Study Information: targeted study information throughout the duration of the study.
- Visit Schedule: site visit reminder as predefined in the Schedule of Assessments.
- Goals: ability to implement study defined or personal goal targets (e.g., exercise, sleep, etc.).
- Reminders: reminders for activities/task relevant to study compliance.

- Notes: journal functions for self-tracking information.

The App is available for down load to patients' smartphone devices that support iOS and Android. The app will contain study-specific information only once activated by a patient. The study coordinator will provide the patient with a secure activation code, which they can use to activate the app upon their first use.

The App does not collect any patient identifiable information or clinical data. This app is intended for informational purposes only. It is not a substitute for professional medical advice. Patients should contact the study site Investigator or coordinator with any medical questions or concerns.

4.4.4 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (basmisanil and placebo) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

- The identification of the Patient to whom the study drug was dispensed (for example, patient initials and date of birth).
- The date(s), quantity of the study drug dispensed to the Patient when out-patient.
- The date(s) and quantity of the study drug returned by the Patient when out-patient.
- All records and drug supplies must be available for inspection by the Roche Monitor [at every monitoring visit].

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, destroyed and provided that adequate storage and integrity of drug has been confirmed.

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

Written documentation of destruction must contain the following:

- Identity (e.g., MEDNO) of investigational product[s] destroyed.
- Quantity of investigational product[s] destroyed.
- Date of destruction.
- Method of destruction.
- Name and signature of responsible person [or company] who destroyed investigational product[s].

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

4.4.5 Post-Trial Access to Basmisanil

The Sponsor does not intend to provide basmisanil or other study interventions to patients after conclusion of the study or any earlier patient withdrawal.

4.5 CONCOMITANT THERAPY AND FOOD

4.5.1 Permitted Therapy

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter (OTC) drugs, approved dietary and herbal supplements, nutritional supplements and any non-medication interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy) used by a patient from screening until the follow-up visit. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

All medication administered to manage AEs (including extrapyramidal symptoms such as dyskinesia or akathisia) should also be recorded on the Adverse Event eCRF.

Allowed concomitant therapy, including medications used for the treatment of *chronic* medical conditions other than schizophrenia that are allowed, must be on a stable dosing regimen for 6 weeks prior to screening and remain stable throughout the study (from screening to last follow-up visit). *Dose adjustments that are required as part of routine treatment to control the chronic condition (such as dose adjustments of insulin or anti-hypertensive medication) are permitted.* Any changes in antipsychotic therapy, for management of worsening of symptoms or initiation of additional pharmacotherapy including antidepressant after randomization may be permitted on a case by case basis, in consultation between the PI and the Medical Monitor/Sponsor. The reason for such changes should be appropriately documented.

Permitted with considerations

Alcohol

- The consumption of alcohol while taking basmisanil is not recommended.

[redacted]

CYP3A substrates

- Basmisanil is a weak, time-dependent inhibitor of CYP3A4 activity. Thus, it is anticipated that pharmacokinetic DDIs between basmisanil and concomitantly administered CYP3A substrates will only be potentially clinically relevant where the CYP3A substrate has a narrow therapeutic window (e.g., alfentanil, astemizole, ergotamine).

4.5.2 Prohibited Therapy

All medications (prescription and OTC) taken from screening to the end of the follow-up period will be recorded on the appropriate eCRF page.

Prohibited therapies should not be administered during the time period from at least 5 days (or 5 half-lives, whichever is longer) prior to initiation of study treatment until the end of the follow-up period, unless otherwise specified.

GABAergic medications

There is the potential for interactions to occur between basmisanil and other compounds whose effects are mediated via $GABA_A$ receptors. Because of the potential for basmisanil to compromise effectiveness of the GABAergic medications (i.e., a higher dose may be required to achieve the desired effect) and vice versa, use of the agents listed below will not be permitted during the study, from screening to the end of the follow-up period:

- General use of $GABA_A$ PAMs (e.g., barbiturates, benzodiazepines and benzodiazepine-related drugs). The use of these agents will be permitted for insomnia and anxiety/agitation with the restrictions described below:
  - For insomnia: Zolpidem up 10 mg/d.
  - For anxiety/agitation: Lorazepam PRN usage permitted with a maximum of 2 mg/week.

  - $GABA_A$ PAMs must not be used within 12 hours of any cognitive assessment. At every visit when cognitive testing is scheduled as per Appendix 1, benzodiazepine intake will be evaluated by asking the patient about his consumption in the past week, and benzodiazepine blood levels will be measured (see Section 4.6.1.5).
- GABA transaminase inhibitors (e.g., phenelzine, valproic acid and vigabatrin).
- GABA reuptake inhibitors (e.g., tiagabine).
- Other anxiolytics, hypnotics and sedatives (e.g., chloral hydrate, ethchlorvynol, meprobamate, methaqualone, paraldehyde). Low doses of trazodone or mirtazapine at night as 'sleep aid pill', or hydroxyzine, are allowed.
- Anesthetics (e.g., chloroform, desflurane, etomidate, ketamine, propofol).
- $GABA_A$ antagonists (e.g., flumazenil). Note: emergency use will require the subject to withdraw from the study.
- GABA dietary supplements.
- Other medications that could have a pharmacodynamic interaction with basmisanil: gabapentin, pregabalin, lamotrigine, topiramate.

Modulators of CYP3A4 Activity

Basmisanil is predominantly cleared by metabolism via CYP3A4 and concomitant medications which significantly alter CYP3A4 activity will affect the PK of basmisanil. Following inhibition of CYP3A4 with itraconazole (study WP29402), the systemic exposure (146 μg • h/mL) and maximum plasma concentration (14.5 μg/mL) of 240 mg BID basmisanil was 4.7- and 4.1-fold higher, respectively. This was associated with a maximum mean ΔQTcF increase of 11.6 msec (90% CI: 5.3 to 17.9). These medications which are prohibited include:

- Moderate or strong inhibitors of CYP3A4 (e.g., itraconazole, erythromycin, fluconazole, nefazodone, ritonavir, verapamil, grapefruit or grapefruit juice).
- Inducers of CYP3A4 (e.g., rifampicin, carbamazepine, pioglitazone, rifampin, modafinil, systemic glucocorticoids, St John's Wort. (Please refer to Appendix 3 for a more detailed list of CYP3A4 inhibitors and inducers).
  - For inducers of CYP3A4, the washout window rule is to stop treatment 30 days or 5 half-lives prior to study drug administration, whichever is longer.

In case concomitant medications are needed that are moderate or strong CYP3A4 inhibitors, the patient should be withdrawn from the study.

Methods of administration which do not produce appreciable systemic drug exposure (e.g., topical administration for skin conditions) are permitted.

[redacted]

Diphenhydramine

Diphenhydramine is not permitted because of potential cardiac effects.

Dofetilide

Dofetilide use is not permitted because of the potential for interaction between basmisanil and renally-cleared cationic drugs, as well as the very narrow therapeutic window of dofetilide.

Anticholinergic medications

Anticholinergic (e.g. benztropine, biperiden, or trihexyphenidyl) are prohibited during the trial due to potential negative impact on cognition and the potential to interfere with the study primary endpoint. Anticholinergics prescribed as prophylaxis treatment for extrapyramidal symptoms need to be washed-out prior to enrollment. If deemed necessary by the PI, beta blockers (e.g. propranolol) can be prescribed instead.

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

At each visit, assessments and examinations will be conducted as described in the Schedule of Assessments (Appendix 1).

The first approximately 40 eligible patients will be enrolled in the study as in-patients and will remain under supervision in the hospital for the first week of dosing. During this period, additional assessments will be conducted as described in the Schedule of Assessments (Appendix 1).

4.6.1.1 Medical and Psychiatric History and Demographic Data

Medical history includes clinically significant diseases, prior medical interventions (e.g., surgeries), smoking/substance use history and prior functional status. All medication (e.g., prescription drugs, OTC drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 5 weeks leading up to the screening visit will also be collected. Psychiatric history includes age at onset of illness, age at first hospitalizations, number of hospitalizations and date of most recent hospitalizations.

Demographic data collected will include age, sex and race/ethnicity (as reported by the caregiver and where applicable). The number of years of education completed by the patient and by the parents will also be collected.

4.6.1.2 Physical Examinations

A general physical exam will be performed as outlined in the Schedule of Assessments (Appendix 1).

Any abnormality identified should be recorded on the Medical History eCRF. Any new or worsened clinically significant abnormality should be reported as AEs on the Adverse Events eCRF. Height and weight will be recorded, and BMI will be calculated.

4.6.1.3 Vital Signs

Vital signs will include measurements of temperature, PR, and SBP and DBP while the patient is in a seated position after the patient has been resting for approximately 5 minutes at each visit. Vital signs should be measured prior to blood draw or at least 10 minutes after the last blood draw. When possible, the same arm should be used for all BP measurements.

BP, PR, and body temperature will be recorded at the time-points specified in the Schedule of Assessments (Appendix 1).

BP and PR measurements should be obtained in a quiet room at a comfortable temperature, with the patient's arm unconstrained by clothing or other material. All measurements will be obtained from the same arm and, with the same cuff size, using a well-calibrated automatic instrument with a digital readout, throughout the study.

4.6.1.4 Electrocardiograms

Triplicate ECG recordings (i.e., three useful ECGs without artifacts) will be obtained within approximately 2-5 minutes at each specified time-point as listed in the Schedule of Assessments (Appendix 1). The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Whenever possible, the same brand/model of a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements should be used for each patient. The conditions should be as close as possible to pre-dose time-points; this includes but is not limited to food intake, activity level, stressors and room temperature.

To minimize variability, it is important that patients be in a resting position for $\geq$ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to meals and any scheduled vital sign measurements and blood draws. In some cases, it may be

appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the patient's permanent study file at the site. ECGs will be reviewed by a central laboratory.

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction), QTcF (Fridericia's correction) and RR will be calculated by the Sponsor/recorded on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

4.6.1.5 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at time-points specified in the Schedule of Assessments (Appendix 1).

Additional samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient's safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility. If there is an alternative explanation for a positive test for drugs of abuse, e.g., previous occasional intake of a medication or food-containing for example, codeine, benzodiazepines or opiates, the test could be repeated to confirm washout. *Furthermore, in case of a positive test for a drug of abuse at screening, that can be explained by a prescribed and permitted co-medication (see Section 4.5.1), a positive result at screening is not systematically exclusionary and will be evaluated on a case by case basis*

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

Samples collected before dosing or from patients on placebo are to be taken as a precautionary measure and may not be analyzed in the first instance.

Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Hematology (leukocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells]).
- Serum chemistry (sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, lactate dehydrogenase [LDH]).
- Coagulation (international normalized ratio [INR], activated partial thromboplastin time [aPTT], prothrombin test [PT]).
- Viral serology
    - HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody).
    - Hepatitis B *(*surface antigen (HBsAg *determines HBV positivity;* *t*otal hepatitis B core antibody (HBcAb) *results do not contribute to eligibility assessment.)*
    - Hepatitis C virus (HCV) antibody. In cases where hepatitis C was successfully treated, a positive HCV serology result can be followed by HCV RNA testing
- Lipids (cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides).
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a blood or urine pregnancy test as outlined in the Schedule of Assessments (Appendix 1).
- Drug and alcohol screen:
- Urine *or saliva* drug screen will be performed at time points indicated in Appendix 1. Agents tested for are *at minimum*: opiates, amphetamines, cocaine, hallucinogens, PCP, *and* cannabis and alcohol. An alcohol *saliva* test can be performed at any time during the study at the PIs discretion.
- Benzodiazepine assessment: Benzodiazepine levels will be measured in blood samples as described in Appendix 1 (see Section 4.5.2 on use of $GABA_A$ PAMs).

4.6.1.6 Pharmacokinetic Assessments

Samples for population PK will be collected on all randomized patients in this study. All patients entering the study will have blood samples taken as described in Appendix 1. All pre-dose samples should be scheduled to occur at a time which would not significantly delay the time a patient is regularly taking the study medication. Samples will be analyzed for basmisanil (and M1 and other metabolites, if relevant).

4.6.1.7 Genotyping and Biomarker Assessments

Two whole blood samples will be collected for (1) Research Biosample Repository (RBR) long-term storage for e.g., future genotyping for consortia contributions (Section 4.6.1.9)

and (2) DNA extraction for genotyping those genes associated with cognition, brain plasticity, and GABA- and glutamatergic functioning, as well as the complement C4 CNVs.

4.6.1.8 Disease-Specific Assessments

Mini International Neuropsychiatric Interview

The Mini International Neuropsychiatric Interview (MINI) (Sheehan 1998) is a structured diagnostic interview designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials. It is a method of organizing a psychiatric interview to make sure all relevant diagnoses are considered. The MINI has been validated against the Structured Clinical Interview for DSM diagnoses. The interview with the patient will be conducted by a trained psychiatrist. Administration time is approximately 20 minutes.

Wide Range Achievement Test 4 (WRAT-4) – Reading Test

The WRAT-4 (Wilkinson et al 2006) reading test measures basic reading skills. The test covers ages from 5 to 75 years old and takes approximately 15-30 minutes to administer. WRAT-reading test will be administered according to standard instructions, at screening only. The age-corrected standard score obtained will be used as pre-morbid IQ estimate.

The WRAT-4 test will be audio- and video-recorded at Screening Visit for quality control purposes. The patient's face will not be visible on the recordings.

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

The WASI-II is an intelligence test designed to estimate IQ in individuals aged 6 to 90 years (Wechsler 2011). The FSIQ score of the four-subtest form will be derived based on the total combined performance on the Vocabulary, Similarities, Block Design and Matrix Reasoning subtests. A Verbal Comprehension Index (VCI) (Vocabulary and Similarities subtests) and a Perceptual Reasoning Index (PRI) (Block Design, Matrix Reasoning subtests) will also be derived. The WASI-II four subtest form should take approximately 30 minutes to administer.

MATRICS Consensus Cognitive Battery (MCCB)

The MATRICS initiative has established a regulatory pathway for the use of the MCCB as cognitive outcome measure in CIAS clinical trials. This comprehensive cognitive battery provides a relatively brief evaluation of cognitive domains relevant to schizophrenia and related disorders (Nuechterlein et al 2008). It was designed to measure seven cognitive domains:

- Speed of processing: Brief Assessment of Cognition in Schizophrenia (BACS) symbol-coding; TMT-A; Category Fluency: animal naming.
- Attention/vigilance: Continuous Performance Test (including identical pairs).
- Working Memory: Spatial Span, Letter Number Span.
- Verbal learning and memory: Hopkins Verbal Learning Test -Revised.

- Visual learning and memory: Brief Visuospatial Memory Test.
- Reasoning and problem solving: Maze Test.
- Social cognition: Emotional Intelligence Test.

Composite scores for each cognitive domain described above, as well as the neurocognitive composite score, which includes all but the social cognition domain, will be derived. The MCCB takes between 60 and 90 minutes to complete.

A clear practice effect has been reported in the literature for the MCCB, therefore the test will be administered twice prior to the formal baseline. In addition, previous exposure to the test will also be recorded (i.e. “has the MCCB ever been administered to the subject before?”, “if yes, how many times and date of last administration”).

The MCCB testing will be audio- and video-recorded at each visit for quality control purposes and for the purpose of obtaining measures of semantic priming (see Semantic Priming below). Of note, the patient will not be visible on the recordings.

The time of the MCCB testing should as far as possible remain the same throughout the study visits (i.e. +/- 30 minutes around the time recorded at the baseline 1 visit), preferably before the lunch meal.

Primacy and Recency Region Effects in Episodic Memory

For the Hopkins Verbal Learning Test – Revised (see MCCB), the number of correctly recalled words in the immediate condition from the primacy (initial 25% of items) and recency (last 25% of items) regions will be noted and supplied to the Sponsor for analyses of learning and recall performance from the primacy and recency regions.

Semantic Priming

Audio recording of the category fluency test (see MCCB), Category Fluency: Animal Naming will be provided to the Sponsor for semantic fluency analysis of consecutively produced words.

Trail Making Test (TMT)

The TMT consists of two parts: Trail making Part A, which is a part of the standard MCCB and Trail making Part B additionally included in this study. Circles containing numbers (Part A) or both numbers and letters (Part B) must be sequentially connected. The total score is the time spent to complete each part. TMT-A involves attention, visual search, motor functioning, and working memory and TMT-B additionally involves executive function. The difference (ratio) in performance between Part A and Part B reflects executive processes and will be used to assess executive functioning including cognitive set shifting abilities. This test should take 5 minutes to complete.

Wechsler Memory Scale - Fourth Edition, Verbal Paired Associates (WMS IV-PAL)

The paired associates learning (I and II) of the WMS-IV (Wechsler 2009) is a test of verbal learning and memory that requires the subject to learn novel word pairs. The subject learns the word pairs across learning trials and is asked to recall them immediately (PAL I) or after a 30-minute delay (PAL II). This test should take approximately 10 minutes to complete.

Wechsler Memory Scale - Fourth Edition, Logical Memory Test (WMS IV-LM)

Logical memory (LM) assesses narrative memory under free-recall conditions. Two short stories are presented orally. The examinee is asked to retell each story from memory immediately after hearing it (LM I). In the delayed condition (LM II), the examinee is asked to retell both stories from the immediate condition (delayed free recall). Each story contains 25 scorable units of information. Different stories will be used across visits: both WMS-IV LM stories will be presented at screening, while 2 different Sullivan LM (2005) stories will be administered at each of the following LM visits (i.e. baseline, week 12 and week 24). This test takes approximately 10 minutes to complete.

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

The CGI (Guy 1976) is one of the most commonly used outcome measures in psychopharmacology clinical trials. The CGI is the general name for two scales: the CGI-Severity scale (CGI-S), which measures global severity of illness at a given point in time and the CGI improvement scale (CGI-I), which measures change from the baseline state at following visits. The CGI rating scale permits a global evaluation by the clinician of the subject's improvement over time. The CGI-S is a 7-point scale ranging from 1 (no symptoms) to 7 (very severe). The CGI-I is a seven-point scale, ranging from 1 (very much improved) to 7 (very much worse).

Personal and Social Performance scale (PSP)

The PSP (Morosini et al 2000) is a scale developed on the basis of the social functioning component of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS). The PSP is a 100-point, single-item rating scale subdivided into 10 equal intervals. The ratings are based upon assessment of the subject's functioning four main areas: 1) socially useful activities; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors.

Virtual Reality Functional Capacity Assessment Tool (VRFCAT)

The VRFCAT (Ruse et al 2014, Keefe et al 2016) is a virtual reality shopping trip performed on a windows computer. Prior to the performance of the task, a brief tutorial version of the VRFCAT, including a mouse usage tutorial administered with a short recipe. This tutorial (15 min) needs to be administered to all participants, regardless of their statements regarding computer familiarity. The task has several linked and sequential scenarios, including matching a recipe to the content of kitchen cabinets, preparing a shopping list, taking the correct bus, shopping efficiently, and catching the

correct return bus. These tasks are performed in a fixed sequence. Multiple forms of the VRFCAT exist; two versions (1 or 4) will be administered alternatively. All data are collected by the computer.

Once the task is launched, it operates itself continuously until the end of the procedure. As with all computerized assessments, the tester will be required to remain vigilant in order to ensure that the participant is continuously engaged in the task. This test should take approximately 30 minutes to complete.

University of Miami Computerized Functional Assessment System (CFAS)

The CFAS consists of four computerized simulations administered on a Windows PC. These simulations include ATM Banking, Telephone Voice Prescription Refill, Transit Ticket Purchase, and Doctors Visit. Data are collected automatically by the computer and are uploaded manually after each visit. At each testing session, a demographic information collection process takes place. Once each task is launched, there is no more input from the tester unless the task needs to be interrupted.

ATM Task: In this task, the participant engages in a series of banking transactions, including enter a PIN, choosing a language, checking balances, transferring money, and withdrawals. The task administers the banking tasks in a fixed order and the task ends itself when the participant reaches the end.

Refill Task: In this task, the participant uses a telephone keypad to access a voice menu to refill two prescriptions. The participant is asked to select a language, enter the prescription number, and choose a time for pickup. The process is repeated for the second prescription.

Transit Ticket Purchase: In this task, the participant uses a ticket kiosk to make a series of purchases in responses to situational requirements. The individual is asked to purchase single and multi-day tickets and to reload a fare card. Each of these task requirements is presented on the computer screen and the participant makes response selections following those instructions.

Doctor’s Visit: In this task, a simulated doctor’s visit occurs with five prescriptions being provided to the participant. The participant then is asked a series of questions about the prescriptions. They then are presented with a package insert for a new medication and asked questions about it. Next, they are asked to prepare a day’s worth of pills in a medication organizer. The task ends with the doctor providing information about the next visit and querying the participant regarding the requirements for that visit.

All subjects are expected to attempt all aspects of the tasks. For participants who claim no experience, the task serves as a problem-solving and skills-learning exercise.

Note that the CFAS should be administered after the VRFCAT, because the VRFCAT has a mouse-use tutorial. The familiarity questionnaire should be completed in all cases, including reported familiarity with each task in the real world as well as experience with computers. The CFAS should take approximately 15 minutes to complete.

Work Readiness Questionnaire (WoRQ)

The WoRQ v4.0 (Potkin et al 2016) captures the patient's capacity to initiate and maintain useful activity that could merit pay – or work readiness – as evaluated by the patient's ability to conduct daily activities, interact with others and adhere to treatment, as well as on others' perceptions of patient appearance, behavior, and impulse control. The questionnaire is composed of 7 items graded "strongly agree," "agree," "disagree," or "strongly disagree," to be completed using progress notes, medical records and input from informants, leading to a final dichotomous work readiness judgment, independent of current work status. The WoRQ requires an average completion time of < 5 minutes.

Schizophrenia Cognition Rating Scale (SCoRS)

The SCoRS (Keefe et al 2015) is an interview-based 20-item rating scale of daily functioning related to cognitive impairment that involves both patients and informants. Each item is rated on a 4-point scale. The SCoRS comprises an assessment of cognitive functioning based on the opinions of the patient and an informant, and an interviewer's decisions about which source of information is more reliable for each item and the global rating (1-10). SCoRS total scores have been shown to be strongly correlated with cognitive performance, functional outcome, and functional capacity in stable patients with schizophrenia. The SCoRS should take approximately 20 minutes to administer.

Brief Negative Symptom Scale (BNSS)

The BNSS (Strauss et al 2012) is a 13-item instrument designed for clinical trials that measures the severity of negative symptoms in 5 domains (subscales): blunted affect, alogia, asociality, anhedonia, and avolition. All ratings are based on a semi-structured interview with prompts and queries. Items are rated on a 7-point (0-6) scale, with anchor points ranging from the symptom being absent (0) to severe (6). Subscale scores as well as a total score will be derived. This test should take approximately 10-15 minutes to complete.

Positive and Negative Syndrome Scale (PANSS)

The PANSS is a 30-item rating scale which evaluates positive, negative and other symptoms in patients with schizophrenia (Kay et al 1987). The Positive Scale assesses the features exhibited in schizophrenia that are not present in those with a normal mental state. The Negative Scale assesses features that are absent in schizophrenia but that would be present in those with a normal mental state. Other sub-scales assess other aspects of schizophrenia including the overall severity of the disorder and the risk of aggression. Each item is rated on a 7-point scale (1 = absent, 7 = extreme). A total score as well as subscale and factor scores will be derived. It takes approximately 40 minutes to administer.

During in-patient stay, items comprising the “Hostility/Excitement” and “Positive symptoms” factors as defined by Marder (Marder and Chouinard 1997), will be administered (Table 1):

Table 1 Items comprising the “Positive symptoms” and Excitement/Hostility” Marder factors

Positive symptoms factor (8 items)	**P1**	**Delusions**
	P3	**Hallucinatory Behavior**
	P5	**Grandiosity**
	P6	**Suspiciousness**
	N7	**Stereotyped thinking**
	G1	**Somatic concern**
	G9	**Unusual thought content**
	G12	**Lack of judgement and insight**
Excitement/Hostility factor (4 items)	**P4**	**Excitement**
	P7	**Hostility**
	G8	**Uncooperativeness**
	G14	**Poor Impulse Control**

The Schizophrenia Quality of Life Scale - Revision 4 (SQLS-R4)

The SQLS is a schizophrenia-specific quality of life self-report questionnaire (Wilkinson et al 2000). It is intended to assess the psychosocial level (e.g., depressive mood, lack of social interactions etc.) and vitality level (e.g., lack of energy, tiredness, poor memory etc.) of patients with schizophrenia. The SQLS-R4 (Martin & Allan 2007) is the 4th revision made to the SQLS to improve its psychometric properties. It contains 33 items covering two domains: psychosocial (20 items) and vitality (13 items), scored using a Likert-type format. It takes 5-10 minutes to complete.

Nurses’ Observation Scale for In-patients Evaluation (NOSIE-30)

The NOSIE-30 (Honigfeld et al 1966) is a sensitive ward behavior rating scale, designed to assess the behavior of patients on an in-patient unit and is an accurate means of systematically assessing patient status and change from baseline in a clinical trial setting. The scale is rated based on continuous observation, according to the frequency of occurrence of 30 designated behaviours. Six factor scores are obtained: Social Competence, Social Interest, Personal Neatness, Irritability, Manifest Psychosis, and Retardation as well as a composite score. This scale will be administered by nurses to in-patients only.

Extrapyramidal Symptoms Evaluation (ESRS-A)

The presence and severity of extrapyramidal symptoms (EPS) will be evaluated using the ESRS-A (Chouinard et al 2005). The ESRS-A is a 28-item scale, designed to objectively and comprehensively measure EPS. The ratings will be made through a combination of a clinical interview, as well as motor examination by a trained research

physician or research psychologist. The time required to complete this assessment is approximately 10 minutes.

Columbia Suicide Severity Rating Scale (C-SSRS)

The assessment of suicidality will be collected for all patients using the C-SSRS (Posner et al 2011). The C-SSRS is a tool used to assess the lifetime suicidality of a patient (C-SSRS baseline version, to be administered at screening) as well as any new instances of suicidality (C-SSRS since last visit version, at other visits as indicated in Appendix 1). 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.

Smartphone Likert Scale Assessments

Three Likert scales assessing mood, quality of sleep, subjective well-being and cognitive functioning and treatment expectancy will be administered via an android smartphone. Patients will be instructed to fill in the Likert scales at defined time points during the trial.

4.6.1.9 Samples for Research Biosample Repository (RBR)

Overview of the RBR

The Roche RBR is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of these specimens 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.

Specimens will be collected from patients who give specific consent to participate in this optional RBR. Collected specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, AEs, or disease progression.
- To increase knowledge and understanding of disease biology.
- To study drug response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB or Ethics Committee (EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

One whole blood sample will be collected for RBR long-term storage, which may be used e.g., for future genotyping for consortia contributions.

The samples collected for DNA extraction may be used for whole genome sequencing (WGS) and other genetic analysis and may be sent to one or more laboratories for analysis.

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

For all samples, dates of consent and specimen collection should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

RBR specimens will be stored and used until no longer needed or until they are exhausted. The RBR storage period will be in accordance with the IRB/EC‑approved Informed Consent Form and applicable laws (e.g., Health Authority requirements).

The repository specimens will be subject to the confidentiality standards (as described under Confidentiality in Section 8.4).

Confidentiality

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

Patient medical information associated with RBR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Patients will not be identified by

name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or patients unless required by law.

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

Consent to Participate in the RBR

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

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

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

Withdrawal from the RBR

Patients who give consent to provide specimens for the RBR have the right to withdraw their specimens at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the patient's wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study BP39207 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study BP39207. Data already generated before time of withdrawal of consent to RBR will still be used.

Monitoring and Oversight

Specimens collected for the RBR will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in RBR for the purposes of

verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

4.6.2 Timing of Study Assessments

4.6.2.1 Order of Assessments

Cognitive testing

The cognitive testing should be performed at a similar time of day and in the same sequence across all study visits, starting with the MCCB, including the TMT-B, at approximately 11 AM±30 min.

Computerized assessments

Computerized assessments should be performed after the cognitive testing, and the VRFCAT should be performed before the CFAS.

All examinations will be performed according to the Schedule of Assessments as outlined in Appendix 1.

4.6.2.2 Screening and Pre-treatment Assessments

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

An Evaluation to Sign Consent (ESC) form will be used to ensure patients' understanding of the study. The form consists of 6 questions rated on a 0 to 2 scale for the level of understanding and participants are required to score at least 10 out of a possible 12 in order to participate in the study. It may be necessary to review the consent documents with the patient multiple times and repeat the ESC to ensure this degree of comprehension (maximum of 3 times).

All screening and pre-treatment assessments must be completed and reviewed to confirm that patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Rescreening may be allowed once and only after approval by the Translational Medicine Leader or designee.

4.6.2.3 Assessments during Treatment

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

All assessments must be performed according to the Schedule of Assessments (Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the Schedule of Assessments.

4.6.2.4 Early Termination Assessments

If a patient is discontinued from the study early, or in case of early study or site termination decided by the Sponsor, patients will be asked to return to the clinic to complete the FU visit 2, as per Appendix 1, 4 weeks after the last dose of study drug.

4.6.2.5 Follow-Up Assessments

After the study completion/early termination visit, AEs should be followed as outlined in Sections 5.4.3 and 5.6.

4.7 PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

The Investigator has the right to discontinue a patient from basmisanil or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the patient.
- Patient non-compliance.

Patients who fulfill the criteria described in the Stopping Rules (as defined in Section 3.1.2) should be discontinued from the study.

For patients who exhibit a worsening of their underlying medical condition that can be managed on an out-patient basis with adjustment of their background medication, the decision to continue with the study will be made on a case-by-case basis in close consultation between the Investigator, the Medical Monitor, and the Sponsor. A worsening of symptoms of schizophrenia does not necessarily constitute a reason for withdrawal of the subject from the study. Appropriate changes in antipsychotic or other pharmacological (i.e., antidepressants) treatment can be instituted if discussed with and agreed to by the Medical Monitor/Sponsor, and should be recorded in the treatment section of the AE eCRF form.

A hospitalization of the patient does not necessarily constitute a reason for withdrawal of the subject from the study (for instance, a short hospitalization for psychosocial reasons may be acceptable). Each case should be discussed with the Medical Monitor/Sponsor. It should be determined if the patient can continue the study medication while hospitalized. In case study medication cannot be continued while the patient is hospitalized, it should be determined if the hospitalization is of such duration that a continuation in the study after discharge can be justified. The decision should be recorded in the eCRF.

4.7.1.1 Discontinuation from Study Drug

Patient must discontinue study drug if they experience any of the following:

- Pregnancy.
- Cardiovascular events, suspected seizure activity, liver abnormalities, creatinine increases as described in Section 3.1.2.
- Patient unable to continue to comply with study requirements.
- Unblinding of a patient.

Patients who discontinue study drug prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 4.6.2.4). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.7.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

Patients will not be followed for any reason after consent has been withdrawn.

4.7.2 Study and Site Discontinuation

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

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Important new information becomes available that may be relevant to the subject's consent.

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

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

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording the incidence, nature and severity of AEs, including SAEs and non-serious AEs of special interest; measurement of protocol‑specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs and laboratory parameters; and other protocol-specified tests described in Section 5.1.1.

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

5.1.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X‑ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Fatal (i.e., the AE actually causes or leads to death).
- Life-threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death). This does not include any AE that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs in-patient hospitalization (see Section 5.3.5.11).
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to a pre-defined grading criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

- Non-serious AEs of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Also see Section 3.1.2, Stopping Rules.

Non-serious AEs of special interest for this study include the following:

- Suspected seizure activity
- Confirmed QTcF value of CTCAE Grade 2 or 480-500 msec (see Appendix 4)
- Confirmed QTcF value exceeding a change from baseline of 60 msec
- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6.

- Confirmed increase of serum creatinine exceeding 1.5 × ULN.
- Worsening of psychosis.
- Suspected transmission of an infectious agent by the study drug, as defined below:

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

5.1.4 Selected Safety Assessments

Additional safety data will be obtained on the following:

- The ECG parameters HR, PQ (PR), QRS, QT, RR and QTcF, along with information on T- and U-waves.
- Changes in ECG parameters as compared to baseline ECG.
- Incidence of clinically significant ECG abnormalities.
- Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results:
  - Hematology: Hemoglobin, hematocrit, RBCs, platelets, WBCs, differentials (counts): neutrophils, eosinophils, lymphocytes, monocytes, basophils.
  - Blood chemistry: AST, ALT, total and conjugated bilirubin, ALP, albumin, creatinine, urea, total protein, total cholesterol, LDL and HDL cholesterol, triglycerides, sodium, chloride, calcium, phosphate, potassium, glucose (fasting).
  - Urinalysis: protein, blood, glucose, leukocytes, nitrites and pH.
- Changes in extrapyramidal symptoms as assessed by the ESRS-A scale.
- Changes in the positive symptoms and excitement/hostility as assessed by the respective PANSS factors (see Section 4.6.1.8).
- Suicidality assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).
- Psychopathological assessment assessed by the NOSIE.

5.2 SAFETY PLAN

The Safety Plan considers observations made in non-clinical investigations including GLP toxicology studies in rats and dogs and the observations made in clinical trials. Hypothetical considerations are included in the interpretation of non-clinical and clinical data.

The safety monitoring and the frequency of the scheduled visits are described in Appendix 1. All safety data will be reviewed throughout the study by the Sponsor in a treatment-blinded manner. However, the safety IMC will review the unblinded safety data obtained during the in-patient stay of the first 40 patients. The following sections specify

some of the monitoring measures that will be taken to maximize the participant's safety in this study.

5.2.1 Management of Specific Adverse Events

5.2.1.1 Changes in Heart Rate and Blood Pressure

Despite the increases in heart rate and BP observed in preclinical and Phase I studies (see Sections [redacted] and 1.2.2.1), similar results were not observed in the MAD study in Down syndrome subjects (Study BP25543) nor in the safety review of BP27832 (CLEMATIS). Vital signs and ECG assessment of the heart rate will be performed throughout the study. Additional assessments of vital signs might be considered by the Investigator.

5.2.1.2 Changes in QTcF Interval

Increased QTcF intervals at supratherapeutic plasma concentrations have been observed in the context of the basmisanil DDI study with itraconazole, a strong CYP3A4 inhibitor. The average maximum concentration was ~ 4-fold higher than the anticipated exposure with 240 mg BID in the current study. Following dosing of basmisanil up to 360 mg BID in the absence of a CYP3A4 inhibitor, categorical analyses of QTc change do not point at a clinically relevant effect and there was no subject with a QTcF interval above 500 msec or with a change from baseline by more than 60 msec. Since patients with schizophrenia may be receiving atypical antipsychotics which may prolong QTc, QTc interval will be monitored at the initiation of basmisanil treatment to address this risk.

ECG recordings are part of the safety monitoring of this study. Stopping rules are provided in line with Roche standard procedures (see Section 3.1.2).

5.2.1.3 Increases in Serum Creatinine

A mild increase in serum creatinine not exceeding the ULN and without concomitant changes in BUN and electrolytes, respectively, was observed in previous clinical trials in healthy volunteers and in people with Down syndrome. Since the increases in serum creatinine have not been associated with changes of other GFR markers, it is likely related to inhibitory effects of basmisanil on the tubular creatinine transporters as shown *in vitro*. In this study, serum creatinine will be measured at various time-points and an increase exceeding $\times$ 1.5 ULN that is confirmed by a repeat testing within three days will result in withdrawal.

5.2.1.4 Suicidality

Clinical experience does not point to any suicidality liability of basmisanil. However, monitoring for suicidality (see C-SSRS in Section 4.6.1.8) is mandatory in clinical trials of CNS active molecules and will be implemented as outlined in Appendix 1 with the C-SSRS. The Investigator is asked to assess individually appropriate next steps in case a suicidality alert arises.

5.2.1.5 Withdrawal Symptoms

At the current time, neither non-clinical nor clinical observations point to a liability of withdrawal symptoms after stopping basmisanil treatment. Nevertheless, AE monitoring (including a phone call by the Investigator 7 days after the last dose) is continued for about 4 weeks after the last dose which is considered appropriate in the context of a dominant half-life of less than 12 hours. Should withdrawal symptoms occur, symptomatic treatment is recommended. Reintroducing basmisanil is not foreseen.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all AEs (see Section 5.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4-5.6.

For each AE recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies). Any other adverse event should not be reported.

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until 4 weeks after the last dose of study drug.

After this period, Investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

Table 2 provides guidance for assessing AE severity.

Table 2 Adverse Event Severity Grading Scale

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

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.1.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs

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

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

A recurrent AE is one that resolves between patient evaluation time-points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($\geq 2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (see Section 3.1.2). Therefore, Investigators must report as an AE the occurrence of either of the following:

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

5.3.5.7 Deaths

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

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within one hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death.

5.3.5.8 Preexisting Medical Conditions

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

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.9 Worsening of Symptoms Associated with Schizophrenia

Worsening of symptoms associated with schizophrenia should be recorded as an AE if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of symptoms associated with schizophrenia on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable specific descriptors (e.g., exacerbation of psychotic symptoms of schizophrenia characterized by “increase of auditory hallucinations”).

A worsening of symptoms of schizophrenia does not necessarily constitute a reason for withdrawal of the subject from the study. Appropriate changes in antipsychotic or other pharmacological (i.e., antidepressants) treatment can be instituted if discussed with and agreed to by the Medical Monitor/Sponsor, and should be recorded in the treatment section of the AE eCRF form.

5.3.5.10 New occurrence or worsening of Extrapyramidal Symptoms (EPS)

Worsening of extrapyramidal symptoms associated with antipsychotic treatment and/or wash-out of prohibited medication should be recorded as an AE if judged by the Investigator to have worsened in severity or frequency or changed in nature at any time during the study.

New occurrence or worsening of EPS does not necessarily constitute a reason for withdrawal of the subject from the study. Appropriate decrease in antipsychotic medication dosage or other pharmacological (i.e., propanolol) treatment can be instituted if discussed with and agreed to by the Medical Monitor/Sponsor, and should be recorded in the treatment section of the AE eCRF form.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAEs in Section 5.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Planned hospitalization required by the protocol.
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The patient has not suffered an AE.
    - Prolonged hospitalization due to psychosocial issues such as lack of home care facilities, caregiver issues, transport issues, etc.

The following hospitalization scenarios are not considered to be SAEs, but should be reported as AEs instead:

- Hospitalization for an AE that would ordinarily have been treated in an out-patient setting had an out-patient clinic been available.

A hospitalization of the patient does not necessarily constitute a reason for withdrawal of the patient from the study (for instance, a short hospitalization for psychosocial reasons may be acceptable). Each case should be discussed with the Medical Monitor/Sponsor. It should be determined if the patient can continue the study medication while hospitalized. In case study medication cannot be continued while the patient is hospitalized, it should be determined whether the hospitalization is of such duration that a continuation in the study after discharge can be justified. The decision should be recorded in the eCRF.

5.3.5.12 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Additional Observations eCRF.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Appropriate supportive treatment should be initiated according to the individual's clinical signs and symptoms and in accordance with best medical practices. *In vitro* studies have shown that benzodiazepines compete with basmisanil for binding to $GABA_A$ receptors, and flumazenil was also able to block the inhibitory effect of basmisanil on GABA-induced currents. Benzodiazepines may therefore be considered as a treatment option for the management of basmisanil overdose.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- SAEs.

- Non-serious AEs of special interest (see Section 5.1.3).
- Pregnancies.

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

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

Investigators must also comply with local requirements for reporting SAEs to the local Health Authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical monitors is available 24 hours a day 7 days a week. Medical monitors contact details are listed in the "Protocol Administrative and Contact Information & List of Investigators".

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of SAEs and non-serious AEs of special interest (see Sections 5.1.2 and 5.1.3), Investigators should record all case details that can be gathered on the Serious Adverse Event Reporting Form and forward this form to the SAE Responsible within 24 hours.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Participants

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 4 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the participant/caregiver, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy.

5.4.3.2 Pregnancies in Female Partners of Male Study Subjects

Male patients will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 4 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the

Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male study subject exposed to study drug. The pregnant partner will need to sign an Authorization For Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by a male study subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth defects

Any congenital anomaly/birth defect in a child born to a female patient should be classified as a SAE, recorded on the AE eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For SAEs, non-serious AEs of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge

summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Investigator is not required to actively monitor patients for AEs after the end of the AE reporting period (defined as 4 weeks after the last dose of study drug).

If the Investigator becomes aware of any other SAE occurring after the end of the AE reporting period, if the event is believed to be related to prior study drug treatment the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event Reporting Form using the fax number or email address provided to Investigators.

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

The Sponsor will promptly evaluate all SAEs and non-serious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the Basmisanil Investigator's Brochure.

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

Based on current withdrawal rates, approximately 231 patients will be enrolled in the study, to ensure that a minimum of 150 patients (50 patients per treatment arm) will have evaluable data at 24 weeks. They will be randomized 1:1:1 to the three study arms.

A sample size of 50 patients per arm provides 80% power to detect a treatment effect size of 0.5, at a 2-sided α-level of 0.1, for the pairwise comparison of each active dose arm to placebo. No adjustments for multiple comparisons will be incorporated into the analysis. Incorporating an assumed withdrawal rate of 35%, a study sample size of 231 (77 patients per arm) will be used. The sample size may be increased if the actual withdrawal rate is higher than expected.

6.2 SUMMARIES OF CONDUCT OF STUDY

To determine whether the integrity of the study was maintained, listing/summary of data referring to the general conduct of the study (such as enrollment, protocol violations, use of prohibited co-medication, blinding details) will be generated.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

All patients who have received at least one administration of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis. For the safety analysis population, data will be analyzed according to the treatment actually taken.

6.3.2 Efficacy Analysis Population

The following analysis populations will be defined: intent-to-treat (ITT) and per-protocol (PP). For both populations**,** patients will be grouped according to the treatment actually taken.

Intent-to-treat Population

The ITT population is defined as consisting of all patients randomized, who received at least one administration of the study treatment and had a baseline and at least one post-dose assessment.

Per-Protocol Population

The PP population will be precisely defined in *a separate document*, before database closure, as the subset of the ITT population without major protocol deviations.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographics, baseline characteristics and all baseline laboratory values will be summarized descriptively by treatment using frequency tables and summary statistics as appropriate.

6.5 SAFETY ANALYSES

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

As appropriate, listings, summary tables and graphs will be provided for safety and tolerability assessments, including:

- Incidence of AEs (overall, by intensity and by relationship to study medication).
- Incidence of SAEs.
- Incidence of laboratory abnormalities (including hematology, clinical chemistry, and urinalysis parameters).
- Incidence of BP abnormalities.

- Incidence of ECG abnormalities as well ECG changes as compared to baseline measurements.
- Changes in the PANSS as compared to baseline.
- NOSIE-30 as compared to baseline.
- Changes in C-SSRS as compared to baseline.

Further details on the safety parameters are given in Section 5.1. Safety data will be summarized using descriptive statistics using the safety analysis population, which will include all patients treated.

6.5.1 Adverse Events

The original terms recorded on the eCRF by the Investigator for AEs will be standardized by the Sponsor.

AEs will be summarized by mapped term and appropriate thesaurus level.

6.5.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Patient listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges.

6.5.2.1 Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

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

6.5.2.2 Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche pre-defined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in patient listings of laboratory data.

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

6.5.3 Vital Signs

Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

6.5.4 ECG Data Analysis

ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

6.5.5 Concomitant Medications

The original terms recorded on the patients' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms.

Concomitant medications will be presented in summary tables and listings.

6.6 EFFICACY ANALYSES

The primary analysis population for all efficacy analyses will be based on the ITT population, which will include all randomized patients treated with study medication.

6.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Cognition assessed by the mean change from baseline in the MCCB neurocognitive composite score

The primary efficacy endpoint (change from baseline to Week 24 in MCCB neurocognitive composite score) will be analyzed using a mixed effect model for repeated measures (MMRM) with treatment, region, age group, sex, schizophrenia cognitive subtype, and visit as fixed effects, treatment-by-visit interaction term, and baseline value as the covariate. The model will include subject as a random effect, and incorporate an unstructured variance-covariance matrix. For each active dose arm tested at the final analysis, this model will be used to test the null hypothesis of no

treatment difference between the placebo arm and the active arm at a 2-sided α-level of 0.1.

6.6.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Mean change from baseline in MCCB cognitive domain scores (attention, speed of processing, reasoning, working memory, visual learning, verbal learning and social cognition).
- Mean change from baseline in the WMS IV-PAL score.
- Mean change from baseline in the WMS IV-LM score.
- Mean change from baseline in the ratio between TMT-B and TMT-A scores.
- Mean change from baseline in the SCoRS score.
- Mean change from baseline in the CGI-S rating.
- Mean change from baseline in the CGI-I rating.
- Mean change from baseline in the PSP total score.

Continuous secondary efficacy endpoints will be analyzed using an MMRM model similar to that described for the primary endpoint, and summarized using descriptive statistics.

6.7 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Individual and mean plasma concentrations at each sampling time-point will be presented by listings and descriptive summary statistics, including means, medians, geometric means, ranges, standard deviations, and coefficients of variation. Individual and mean plasma concentration versus time data will be plotted on semi-logarithmic scales.

Graphical exploration of the relationship between basmisanil (and M1 and other metabolites, if relevant) exposure and outcome measures as well as safety parameters will be performed. If indicated by such exploration, more formal analyses of PK to PD parameters of interest may be undertaken.

6.8 PATIENT-REPORTED OUTCOME ANALYSES

The patient-reported outcomes are:

- Change from baseline on the patient-reported health-related quality of life scale (SQLS).

- Change in subjective mood, sleep and subjective well-being and cognitive functioning ratings.

These endpoints will be analyzed using an MMRM model similar to that described for the primary endpoint, and summarized using descriptive statistics.

6.9 EXPLORATORY ANALYSES

The exploratory analyses will include:

- Mean change from baseline in the PANSS factor and total scores.
- Mean change from baseline in the BNSS subscales and total scores.
- Mean change from baseline in % of patients rated as “ready to work” on the WoRQ.
- Mean change from baseline in the VRFCAT score.
- Mean change from baseline in the CFAS score.
- Semantic priming analysis of verbal fluency, as described in Section 4.6.1.8.
- Primacy region analysis of episodic verbal learning and recall**.** Percentage recall from the primacy relative to the recency region will be calculated for each learning trial and for long-delay free recall.
- Analysis of genetic PRS and complement C4 CNV as described in Section 3.2.3, and the 15q11-q13 chromosomal region including the GABRs GABRB3, GABRB5 and GABRG3 genes.

These endpoints will be analyzed using an MMRM or ANCOVA model as appropriate, and summarized using descriptive statistics.

6.10 INTERIM ANALYSES

An interim analysis will be conducted when approximately 30 patients per arm have completed the first 12 weeks of treatment. The analysis will be conducted by the efficacy IMC as described in Section 3.1.3.2.

This analysis will focus on the change from baseline to Week 12 in MCCB neurocognitive composite score, which will be analyzed using an MMRM model which will be similar to that described for the primary analysis (including all stratification factors although this may not be possible depending on the actual cell size). The pairwise comparison of each active dose to placebo will be evaluated using the estimated effect size based on the least-squares mean (LSM) estimates from the MMRM models. For each dose arm, the decision whether to continue or drop the arm for the remainder of the study will be based on the *conditional* probability that the true treatment effect size

for that arm is ≥ 0.35. If the calculated *conditional* probability is less than 20% that the true treatment effect size can reach this threshold for one of the two doses, then that dose arm may be discontinued. If this *conditional* probability is less than 20% for both dose arms, then the study may be discontinued for futility.

In case the calculated *conditional* probability that the true treatment effect size can reach the threshold of effect size > 0.35 is more than 20% for both treatment arms, one treatment arm may still be discontinued.

Further analysis details on the interim analysis will be documented in a separate Efficacy IMC Agreement Document prior to the conduct of the interim analysis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the Electronic Data Capture (EDC) system.

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.

The Sponsor will produce a Data Handling Manual and a Data Management Plan that describes the quality checking to be performed on the data. Data collected electronically will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Contract research organizations (CROs) may also be responsible for quality checking of the data or parts of the data. In this case and in the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system as appropriate.

If responsible for quality checking of data, the CRO will produce a Data Management Plan or equivalent document that describes the quality checking to be performed on the data. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an on line 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 enrolled, an eCRF must be completed and electronically signed by the PI or authorized delegate from the study staff. 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/CRO in the eCRFs and in all required reports.

eCRFs will be submitted electronically to the Sponsor/CRO and should be handled in accordance with instructions from the Sponsor/CRO.

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the PI for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

In this study, the informant will be asked to provide information useful to assess patient eligibility and to complete clinician rated scales. A separate written informed consent will be obtained from the informant.

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

In this study, the Investigator or Designee shall assess the capacity of the patient to give informed consent while discussing the study and the Consent Forms. This assessment shall be confirmed by the *results of the ESC form (see Inclusion Criteria Section 4.2.2) and the* IQ measure (see Exclusion Criteria*, Section 4.2.3*) done during the Screening Visit.

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

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

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

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. HIPAA of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The PI is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

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

8.4 CONFIDENTIALITY

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

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

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

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLO).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol

amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

Roche shall also submit a Development Safety Update Report (DSUR) once a year to the Independent Ethics Committee (IEC) and Health Authorities according to local regulatory requirements and timelines of each country participating in the study.

It is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, will be reviewed and approved by an IRB. This board must operate in accordance with the current Federal Regulations. The Sponsor will be sent a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments /modifications are made to the protocol. Roche shall also submit an IND Annual Report to the FDA according to local regulatory requirements and timelines.

9.2 SITE INSPECTIONS

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

9.3 ADMINISTRATIVE STRUCTURE

This study will be conducted using the services of a CRO managed by Roche. The CRO will manage the vendors required to provide services such as cardiac monitoring, IXRS, event planning, central laboratories, scale management and cognitive testing and Roche will maintain oversight. The study will utilise an IMC consisting of Roche personnel.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings by the Sponsor or designated Investigators. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. All publications have to be approved by the Sponsor. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

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

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

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

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

9.5 PROTOCOL AMENDMENTS

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

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

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Appendix 1 Schedule of Assessments

Week	Screening[a]	Baseline 1[b]	Baseline 2[a,b]	Week 1			Week 2	Week 4	Week 6	Week 9	Week 12[a]	Week 16	Week 20	Week 24[a]	F-U1 week 26 phone call[l]	F-U2 week 28
Day	(Up to 5 weeks)	(up to Day -14)		Day 1	In-patients only Days 2, 3, 4, 5, 6	Day 7	Day 14	Day 28	Day 42	Day 63	Day 84	Day 112	Day 140	Day 168	Day 182	Day 196
Time Relative (h)	***	***	***	0	***	144	312	648	984	1488	1992	2664	3336	4008	4344	4680
Visit Window						+/-1	+/-2	+/-2	+/-2	+/-2	+/-2	+/-3	+/-3	+/-3	+/-3	+/-3
Assessments																
Informed Consent	X															
Evaluation to Sign Consent (ESC)	X															
Eligibility	X															
Demography	X															
Medical History	X															
Physical Examination	X										X[n]			X		
Urine drug screen	X		X						X		X			X		X
Alcohol testing	X		X						X		X			X		X
Pregnancy test[c]	X										X					X
Vital Signs	X			X[e]	X	X[e,h]	X	X	X	X	X	X	X	X		X
ECG-12 lead (triplicates)[d]	X			X[e]		X[e,h]	X	X	X	X	X	X	X	X		X
Antipsychotic testing	X															
Blood Chemistry	X		X			X	X		X		X	X	X	X		X
Hematology	X		X			X	X		X		X			X		X
Coagulation	X										X					X
Serology	X															X
Urinalysis	X		X								X			X		X
Genotyping			X[k]													
RBR DNA			X[k]													
Administration of Study Medication				X	X	X	X	X	X	X	X	X	X	X[f]		
PK Sample[d]						X[h]	X		X		X			X		
Benzodiazepine sample			X								X			X		X
Benzodiazepine questions			X								X			X		X

Appendix 1 Schedule of Assessments (cont.)

Week	Screening[a]	Baseline 1[b]	Baseline 2[a,b]	Week 1			Week 2	Week 4	Week 6	Week 9	Week 12[a]	Week 16	Week 20	Week 24[a]	F-U1 week 26 phone call[l]	F-U2 week 28
Day	(Up to 5 weeks)	(up to Day -14)		Day 1	In-patients only Days 2, 3, 4, 5, 6	Day 7	Day 14	Day 28	Day 42	Day 63	Day 84	Day 112	Day 140	Day 168	Day 182	Day 196
Time Relative (h)	***	***	***	0	***	144	312	648	984	1488	1992	2664	3336	4008	4344	4680
Visit Window						+/-1	+/-2	+/-2	+/-2	+/-2	+/-2	+/-3	+/-3	+/-3	+/-3	+/-3
Assessments																
MINI	X															
WASI-II 4 subtests[g]	X															
WRAT-4 reading test	X															
MCCB[m]	X	X	X								X			X		X
TMT-part B[m]	X	X	X								X			X		X
SCoRS			X								X			X		X
WMS IV -LM[m]	X		X								X			X		
WMS IV-PAL[m]	X		X								X			X		X
PSP			X								X			X		X
VRFCAT			X								X			X		X
CFAS			X								X			X		X
WoRQ			X								X			X		X
SQLS			X								X			X		X
NOSIE-30[h]			X	X	X	X										
PANSS	X		X	X[i,h]	X[i]	X	X	X	X	X	X	X	X	X		
ESRS-A			X			X			X		X		X	X		X
CGI-S			X		X	X	X	X	X	X	X	X	X	X		
CGI-I					X	X	X	X	X	X	X	X	X	X		
BNSS			X			X	X		X	X	X	X	X	X		X
Assessment of suicidality C-SSRS	X		X			X	X	X	X	X	X	X	X	X	X	X
Weekly contact with patient[j]			X			X	X	X	X	X	X	X	X	X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a) can be split over 2 days if preferred

b) baseline visit 1 and baseline visit 2 should be approximately 1 week apart

c) blood test at screening visit

d) to be taken before the morning dose, unless otherwise specified

e) 2 measures to be taken: 1x pre-dose, 1x 4-5 hours after the morning dose (day 1 and day 7)

f) The morning dose is the last dose for the study, to be taken from the week 20 inventory

g) MCCB and WRAT-4 will be video and audio recorded

h) in-patients only

i) only positive symptoms factor (items P1,P3,P5,P6,N7,G1,G9,G12) and hostility/excitement factor (items P4,P7,G8,G14) will be administered

j) via phone calls when no visit is planned

k) samples can be taken at any time between BL and FU2

l) the FU1 visit will be conducted by phone to assess the patient's general condition.

m) cognitive testing should be performed at a similar time of day and in the same sequence across all study visits, starting with the MCCB

n) body weight only

Appendix 2 Antipsychotics Equivalent Dose

The tables below show the approximate marketed equivalent doses of antipsychotics to up to a maximum of 6 mg risperidone or 600 mg chlorpromazine, respectively. The following principles for the derivation of antipsychotics equivalent doses were applied:

1. The equivalent doses of commonly used antipsychotics follow guidance from relevant clinical literature and the expert consensus guideline for optimizing pharmacologic treatment of psychotic disorders.

2. The table only shows approximate equivalent doses for marketed dose strengths and dose ranges in accordance with the label information available (may vary from country to country). In practice, doses of antipsychotics should be within dose ranges approved by the local Health Authority.

3. In practice, if a dose of a given antipsychotic falls in between two doses in the table, the higher dose should be used.

4. For antipsychotics that are not listed in the table, the Investigator should contact the Medical Monitor before enrolling the patient.

Appendix 2 Antipsychotics Equivalent Dose (cont.)

	Possible Market Dose Strength: mg/tab or cap	Equivalent Marketed Dose of Antipsychotics: mg/day (oral)						
Risperidone	**0.25, 0.5, 1, 2, 3, 4, 5**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**
Chlorpromazine	**25, 50, 100, 200**	**50**	**100**	**150**	**200**	**300**	**400**	**600**
Aripiprazole	2, 5, 10, 15, 20, 30		5		10	15	20	30
Aripiprazole (Japan)	3, 6, 12		3	6		9	15	24
Asenapine	5, 10			5		10		20
Fluphenazine	1, 2.5, 5, 10	1	2		4	6	8	12
Fluphenazine decanoate (monthly)	25						25	50
Fluphenazine enantate (monthly)	25						25	50
Haloperidol	0, 1, 2, 5, 10				3	5	6	10
Haloperidol decanoate (monthly)	50, 100				50		100	150
Iloperidone	1, 2, 4, 6, 8, 10, 12		4		8	12	16	24
Molindone	5, 10, 25, 50	5	10	15	25	35	50	75
Olanzapine	2.5, 5, 7.5, 10, 15, 20		2.5	5	7.5	10	15	20
Paliperidone	1.5, 3, 6, 9, 12		3		6	9	12	15
Paliperidone palmitate (monthly)	39, 78, 117, 234		39		78	117		234
Perphenazine	2, 4, 8, 16	2	6	8	12	16	24	32
Pimozide	1, 2		1	2		4	5	8
Prochlorperazine	5, 10, 25		5		10	15	25	35
Quetiapine (including XR formulation)	25, 50, 100, 200, 400	50	150	200	300	450	600	800 - 1200
Risperidone LA (every 2 weeks)	12.5, 25, 37.5, 50			12.5		25	37.5	50
Thiothixene	1, 2, 5, 10	2	4	6	8	12	16	25
Trifluoperazine	1, 2, 5, 10		5		10	15	20	30
Ziprasidone	20, 40, 60, 80		20	40	60		120	160
Zuclopenthixol	10, 25, 40	10	20	25	25	40	40	50

Appendix 2 Antipsychotics Equivalent Dose (cont.)

	Possible Market Dose Strength: mg/tab or cap	Equivalent Marketed Dose of Antipsychotics: mg/day (oral)						
Risperidone	**0.25, 0.5, 1, 2, 3, 4, 5**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**
Chlorpromazine	**25, 50, 100, 200**	**50**	**100**	**150**	**200**	**300**	**400**	**600**
Amisulpride	50, 100, 200, 400	50	100	150	200	300	400	600
Blonanserin	2, 4	2	4	6	8	12	16	24
Bromperidol	1, 3, 6	1	2	3	4	6	8	12
Carpipramine	25, 50		25	50	75	100	150	225
Chlorprothixene	10, 25, 50, 100	50	100	150	200	300	400	600
Clocapramine	10, 25, 50	10	25	35	50	75	100	150
Clotiapine	40	25	50	75	100	150	200	300
Cyamemazine	25, 100	25	50	75	100	150	200	300
Flupenthixol	3			3		6		12
Flupenthixol decanoate (every 2 weeks)	20 mg/ml (1 ml -10 ml)				20		40	80
Fluspirilence (weekly)	2, 4, 6						4	8
Levomepromazine	25			100		200		400
Loxapine	5, 10, 25, 50	5	15	20	30	45	65	95
Lurasidone	40, 80					40		80
Melperone	25, 50, 100	25	50	100		150	200	300
Mesoridazine	10, 25, 50, 100	25	50	75	100	150	200	300
Mosapramine	10, 25, 50	10	30	50	60	100	130	200
Nemonapride	3, 10		3	6		12	16	25
Olanzapine pamoate (bi-weekly)	210 mg, 310 mg, 405 mg vials					150	210	300
Olanzapine pamoate (monthly)	310 mg, 405 mg vials					300	405	
Oxypertine	20, 40	20	50	70	100	150	200	300
Penfluridol (weekly)	20					20	40	60
Perazine	25	50	100	150	200	300	400	600
Pericyazine	2.5, 10			12.5		25		50
Perospirone	4, 8, 16	4	8	12	16	24	32	48
Perphenazine decanoate (bi-weekly)	50, 100					50		100
Pipamperone	50	50	100	150	200	300	400	600
Pipotiazine palmitate (monthly)	50				50		100	150
Prochlorperazine	5, 10, 25		5		10	15	25	35
Prothipendyl	40, 80	50	100	150	200	300	400	600
Reserpine	0.1, 0.25		0.1	0.25	0.3	0.5	0.6	1
Sertindole	4, 12, 16, 20			4		12	16	20
Spiperone	0.25, 1	0.25	0.75	1	1.5	2.25	3	4.5

Appendix 2 Antipsychotics Equivalent Dose (cont.)

	Possible Market Dose Strength: mg/tab or cap	Equivalent Marketed Dose of Antipsychotics: mg/day (oral)						
Risperidone	**0.25, 0.5, 1, 2, 3, 4, 5**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**
Chlorpromazine	**25, 50, 100, 200**	**50**	**100**	**150**	**200**	**300**	**400**	**600**
Sulpiride	50, 100, 200	100	200	300	400	600	800	1200
Sultopride	50, 100, 200	100	200	300	400	600	800	1200
Thioridazine	10, 25, 50, 100			125		250		500
Tiapride	25 (27.8)		25		50	75	100	150
Timiperone	0.5, 1, 3	0.5	1	2	2.5	4	5	8
Zotepine	25, 50, 100	25	50	100	125	200	250	400
Zuclopenthixol decanoate (bi-weekly)	200 mg/ml		80-150	80-150	150-200	250	300	450
Cariprazine	*1.5, 3, 4.5, 6*			*1.5*		*3*		*6*
Brexpiprazine	*0.25, 0.5, 1, 2, 3, 4*		*0.5*	*1*		*2*		*4*

Appendix 3 Examples of prohibited CYP3A4 inhibitors and inducers concomitant medication

Please note that this is not an exhaustive list of prohibited CYP3A4 inhibitors or inducers.

Strong CYP3A4 Inhibitors:

- Indinavir
- Nelfinavir
- Ritonavir
- Clarithromycin
- Itraconazole
- Ketoconazole
- Nefazodone
- Saquinavir
- Subuxone
- Telithromycin

Moderate CYP3A4 Inhibitors:

- Aprepitant
- Erythromycin
- Fluconazole
- Grapefruit juice
- Verapamil
- Diltiazem

CYP3A4 Inducers

- Efavirenz
- Nevirapine
- Barbiturates
- Carbamazepine
- Enzalutamide
- Glucocorticoids
- Modafinil
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Pioglitazone
- Rifabutin
- Rifampin
- St John's Wort
- Troglitazone

From http://medicine.iupui.edu/CLINPHARM/ddis/main-table

Appendix 4 Common Terminology Criteria for Adverse Events (CTCAE): QTc Criteria

Adverse Event	Investigations				
	Grade				
	1	2	3	4	5
Electrocardiogram QT corrected interval prolonged	QTc 450-480 ms	QTc 481-500 ms	QTc ≥ 501 ms on at least two separate ECGs	QTc ≥ 501 or > 60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-

Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.