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MIJ821

Clinical Trial Protocol CMIJ821X2201

A multi-center, randomized, subject and investigator-blinded, placebo-controlled, active comparator, parallel-group proof of concept study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of MIJ821 in patients with treatment-resistant depression

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APA	American Psychological Association
AR(1)	first-order autoregressive
AST	aspartate aminotransferase
AUC	Area Under the Curve
AUCinf	Area Under the Curve from time zero to infinity
AUClast	area under the curve from time zero to time of last measurable concentration

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BP	Blood Pressure
BRMS	Bech-Rafaelsen Melancholia Scale
BUN	blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CADSS	Clinical-Administered Dissociative States Scale
CFR	U.S. Code of Federal Regulations
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CK	creatinine kinase
CL	apparent total body clearance of the drug from plasma
cm	centimeter(s)
Cmax	maximum plasma drug concentration
CMO&PS	Chief Medical Office & Patient Safety
CNS	Central Nervous System
CO_2	carbon dioxide
CRA	Compliance and Regulatory Affairs
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization

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CSR	Clinical study report
CTC	Common Toxicity Criteria
CV	coefficient of variation
DAE	Dissociative adverse event
DAR	Dose Administration Record
DDE	Direct Data Entry
DES	Dissociative Experiences Scale
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	electronic Case Report Form

EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	Europe
FAS	Full Analysis Set
FIH	First in Human
FSH	Follicle Stimulating Hormone
GASE	Generic Assessment of Side Effects
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
h	Hour
HAM-A	Hamilton Anxiety Rating Scale
HIV	human immunodeficiency virus
hsCRP	High Sensitivity C-Reactive Protein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	Interleukin
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intrauterine system
kg	killogram(s)
KMDRS	Koukopoulos Mixed Depression Rating Scale
KR	Kenward-Roger
LC-MS/MS	Liquid Chromatography-tandem Mass Spectrometry
LDH	lactate dehydrogenase

MADRS	Montgomery Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMDC	Melancholia and Mixed Depression Diagnostic Checklist
MMRM	Mixed-effects Model for Repeated Measures
MTI	Maudsley Treatment Inventory

NIRT	Novartis Interactive Response Technology
NMDA	N-methyl-D-aspartate
NOEL	No Observable Effect Level
PD	pharmacodynamic(s)
PHQ	Patient Health Questionnaire
PK	pharmacokinetic(s)
PPS	per protocol set
QMS	Quality Management System
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell(s)
RoW	Rest of World
SAE	serious adverse event
SCID-5(-RV)	Structured Clinical Interview for DSM-5 (Research Version)
SD	standard deviation
SMPI	Sydney Melancholia Prototype Index
SMQ	Standardized MedDRA Query
SOM	Site Operations Manual
STS	Suicidality Tracking Scale
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1/2	Elimination half-life
Tmax	time to reach maximum plasma concentration
TRD	Treatment-Resistant Depression
TSH	thyroid-stimulating hormone
ULQ	Upper Limit of Quantification
UN	unstructured
US	United States
Vz	apparent volume of distribution during terminal phase
WBC	white blood cell(s)
WHO	World Health Organization
WOC	Withdrawal of consent
β-hCG	Beta-Human Chorionic Gonadotropin

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest for the study
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples
Randomization number	A unique identifier assigned to each randomized subject
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

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Protocol summary

Protocol number	CMIJ821X2201
Full Title	A multi-center, randomized, subject and investigator-blinded, placebo-controlled, active comparator, parallel-group proof of concept study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of MIJ821 in patients with treatment-resistant depression
Brief title	Study of efficacy and safety of MIJ821 in treatment-resistant depression patients.
Sponsor and Clinical Phase	Novartis
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The main purpose of this non-confirmatory study is to evaluate the clinical responses of MIJ821 in patients suffering from treatment-resistant depression assessed by the Montgomery Åsberg Depression Rating Scale (Montgomery and Asberg 1979). Furthermore it is expected that this study will guide the future clinical trials with MIJ821 in treatment of resistant depression.
Primary Objective(s)	The primary objective of this study is to assess the efficacy of MIJ821 in treatment-resistant depression at 24 hours after the start of infusion. The measure will be conducted through MADRS total score, 24 hours after the start of first infusion compared to the baseline assessment.
Secondary Objectives	To assess the efficacy of MIJ821 in treatment-resistant depression by 1) evaluating the percentage of treatment response (>50% improvement in MADRS) at 24 hours, 48 hours (if applicable) and 6 weeks after the start of first infusion 2) evaluating the percentage of remission (MADRS <7) at 24 hours, 48 hours (if applicable) and 6 weeks after the start of first infusion; 3) evaluating the CGI-I and CGI-S scores at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion. To assess the impact of MIJ821 on suicidality. To assess the MIJ821 pharmacokinetics in plasma. To assess the most effective dose and dosing regimen. To assess the safety and tolerability of weekly and bi-weekly infusions of MIJ821. To assess the efficacy in melancholic subtype of depression. To assess the risk of mania induction. To assess the efficacy of MIJ821 for mixed mood symptoms. To assess the efficacy of MIJ821 for anxiety symptoms. To assess the impact of mixed mood symptoms, melancholia, and anxiety as predictors of treatment response to MIJ821.

Study design	This is a multi-center, randomized, parallel group, active comparator, placebo-controlled study. The study will enroll approximately 66 subjects presenting with Treatment-Resistant Depression. The study consists of a screening and baseline period (D-28 to D-1), a treatment period (D1 to D36) and a 5 week follow-up period with an end of study visit on Day 71. The maximum duration of the study including screening is approximately 14 weeks.
Population	Male and female subjects, 18 to 65 years (inclusive), diagnosed with Treatment-Resistant Depression. Eligible subjects may come from either an inpatient or outpatient treatment setting.
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study. • Male and female subjects, 18 to 65 years of age (inclusive) at screening. • Subject is in a DSM-5 defined major depressive episode at the time of screening • Subject obtains a Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥ 24 at screening and baseline • Failure to response to two or more prior antidepressant treatments, where two failed treatments are of two different antidepressants, with adequate dose and duration (≥ 8 weeks duration, doses defined per agent) for the current or prior major depressive episode, as identified by the Maudsley Treatment Inventory, and prior psychiatric history, assessed by the investigator, and further documented by medical records and/or third party report (family, friends, clinician-treaters) where available • At least one prior clinical depressive episode (recurrent major depressive disorder), as identified by prior psychiatric history assessed by the investigator, and further documented by medical records and third party report (family, friends, clinician-treaters) where available.
Key Exclusion criteria	• Any current diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorder. • Current alcohol or substance use disorder (including marijuana and prescribed amphetamine) meeting DSM-5 criteria, within the past month at baseline. Nicotine and caffeine use disorders are not considered as exclusionary substances. • Prior suicidality caused by or associated with ketamine, as identified by prior psychiatric history assessed by the investigator, and augmented by medical records and third party report (family, friends, clinician-treaters) where available. • Acute serious and/or imminent suicidal ideation and/or intent within the prior 2 weeks, or any suicide attempt within the prior 4 weeks at screening. Mild to moderate suicidal ideation, using the Sheehan Suicidal Ideation Scale and not meeting the above definition, is not an exclusion criterion. • Use of other investigational drugs within 30 days or 5 half-lives of randomization, whichever was longer; or longer if required by local regulations. • Current pregnancy or lactation. • Positive HIV, Hepatitis B or C test. • Resting QTcF ≥450 msec (male) or ≥460 msec (female) at pre-treatment baseline.

Study treatment	Patients who meet the eligibility criteria at screening and baseline will be randomized to one of the six treatment arms in the European countries (only five arms in the USA as there is no ketamine arm) Commercially Confidential Information
Efficacy assessments	• Montgomery Åsberg Depression Rating Scale at 24 hours post-dose • % treatment response (>50% improvement in MADRS) at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion • % treatment remission (MADRS<7) at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion • CGI-S and CGI-I scores at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion Sheehan Suicidality Tracking Scale score changes from baseline at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion • Montgomery Åsberg Depression Rating Scale score at 6 weeks after the start of first infusion
Other assessments	Commercially Confidential Information
Pharmacokinetic assessments	MIJ821 pharmacokinetics in plasma
Key safety assessments	Adverse event monitoring, Physical examinations, Monitoring of laboratory markers in blood and urine, ECGs.
Data analysis	The change from baseline in the total MADRS score at 24 hours after single dose administration will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a group factor and baseline MADRS score as a covariate. Commercially Confidential Information
Key words	Treatment-Resistant Depression; Major Depressive Episode; Major Depressive Disorder

1 Introduction

1.1 Background

Treatment-resistant depression (TRD) is defined as a failure to respond to at least two different antidepressants for a period longer than 4-6 weeks at the maximum recommended dose (Sackeim 2001). One-third or more of patients suffering from unipolar depressive illness, defined in DSM-5 as major depressive disorder (MDD), fail to respond acutely to antidepressant treatment of adequate dose and duration (Rush et al 2006). Even more subjects, the majority in fact, fail to maintain long-term response to standard antidepressants (Rush et al 2006). Further, suicide is a major harm with depressive illness, with depression being present in the vast majority of persons who commit suicide (Isometsä 2001). Most antidepressants have a few weeks delay in symptom benefit, during which time individuals can be at suicidal risk.

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Ketamine, which is a NMDA receptor antagonist, has been shown to be effective in TRD in off-label research, but is limited by psychotomimetic side effects (Katalinic et al 2013; Browne and Lucki 2013). Further ketamine has been shown to be rapid-acting and reduce suicidality (Katalinic et al 2013). The efficacy of ketamine provides the rationale for targeting NMDA receptor inhibition as a rapid-onset antidepressant mechanism.

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1.2 Purpose

The main purpose of this non-confirmatory study is to evaluate the clinical responses of MIJ821 in subjects suffering from treatment-resistant depression assessed by the Montgomery Åsberg Depression Rating Scale (Montgomery and Asberg 1979), a validated and widely employed method in depression trials.

Furthermore, it is expected that this study will guide the future clinical trials with MIJ821 in patients with treatment resistant depression.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess efficacy of MIJ821 in treatment-resistant depression.	• Montgomery Asberg Depression Rating Scale total score at 24 hours after the start of the infusion compared to the baseline assessment.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess risk of mania induction.	• Young Mania Rating Scale at 24 hours, 48 hours (if applicable) and 6 weeks post-dose.
• To assess efficacy in the melancholic subtype of depression.	• Bech-Rafaelsen Melancholia and CORE scale change from baseline to 24 hours, 48 hours (if applicable) and 6 weeks post-dose.
• To assess safety and tolerability, especially dissociative side effects.	• Incidence of adverse event Dissociative rating scales (Clinician-Administered Dissociative States Scale, and Dissociative Experiences Scale) change from baseline to 24 hours, 48 hours (if applicable) and 6 weeks post-dose.
• To assess most effective dose and dosing regimen.	• Montgomery Åsberg Depression Rating Scale score at 6 weeks.
• To assess MIJ821 pharmacokinetics in plasma.	• PK properties of MIJ821 in plasma described by AUClast, AUC0-24h, Cmax, Tmax (parameters not limited)
• To assess impact of MIJ821 on suicidality.	• Sheehan Suicidality Tracking Scale changes from baseline at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion.
• To assess efficacy of MIJ821 on measures of response and remission	• % treatment response (>50% improvement in MADRS) at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion. % treatment remission (MADRS<7) at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion CGI-S and CGI-I scores at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion
• To assess efficacy of MIJ821 for mixed mood symptoms.	• Koukopoulos Mixed Depression Rating Scale change from baseline to 24 hours, 48 hours, and 6 weeks after the start of first infusion.
• To assess efficacy of MIJ821 for anxiety symptoms.	• Hamilton Anxiety Scale change from baseline to 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion

Objective(s)	Endpoint(s)
• To assess impact of mixed mood symptoms, melancholia, and anxiety as predictors of treatment response to MIJ821.	• Regression model effect sizes (odds ratios) for Hamilton Anxiety Scale, Bech-Rafaelsen Melancholia Scale, and Koukopoulos Mixed Depression Rating Scale as predictors, with MADRS treatment response as outcome, at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

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3 Study design

This is a non-confirmatory, multi-center, 6-treatment arm in the European countries and 5-treatment arm in the USA (no ketamine arm), randomized, subject and investigator blinded, parallel group, placebo controlled study in treatment-resistant depression patients. The study will randomize approximately 66 Subjects and while the study design utilizes an outpatient visit schedule, the study allows for the inclusion of subjects seeking treatment for their disease from both an 'inpatient' or 'outpatient' clinic setting.

A screening period of maximum 4 weeks will be used to assess eligibility. Patients who meet the eligibility criteria at screening will proceed to baseline evaluations on Day-1 or Day 1. All baseline safety evaluation results must be available prior to randomization. At the baseline visit, eligible subjects will be randomized to one of the treatment arms. Randomized subjects will enter a 36- day treatment period, receiving at each treatment visit, a 40-minute infusion with a safety observation period of 2-4 hours (i.e. a minimum of 2 hours) post the start of

infusion. If the subject reports no dissociative symptoms and no suicidal symptoms, the subject will be allowed to leave the clinical treatment setting. Visits to assess efficacy and safety are scheduled at 24 hours, 48 hours (if applicable) and every week during the treatment period. If 48 hour visit (V103) is conducted, then all assessments should be completed. The assessment to address the primary objective will be performed at 24 hour post-dose. Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring. At the conclusion of the treatment period (Day 1 - Day 36), subjects will enter a 5-week follow up period consisting of two follow visits approximately 1 week (Day 43) and 3 weeks (Day 57) after the last study drug administration and an end of study completion visit (Day 71) The total duration for each subject in the study is maximum 14-weeks including screening and baseline. No interim analysis is planned. The study design is summarized in Figure 3-1 below for the European countries (same study design without the ketamine arm in the USA).

Figure 3-1 Study design

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4 Rationale

4.1 Rationale for study design

The design of this study has been selected to adequately assess the primary objective and follow the similar design of trials for American Psychiatric Association (APA) treatment guidelines for depression (Practice guideline for the treatment of patients with major depressive disorder 2010)

The rationale and justification for the key elements of the study design are as follows:

- Safety of administration of MIJ821 is supported by toxicology studies (i.e. 6-week GLP studies) and by results from a study in healthy volunteers (MIJ821X2101).
- Selection of ketamine 0.5 mg/kg IV infusion is a standard dose shown to have antidepressant effects (Garay et al 2017).
- Randomization to parallel groups controls for confounding factors and allows for more valid cause judgments.
- Blinding with placebo control limits effects of expectation bias or measurement bias.

The entire treatment period (36 days) can be conducted in an outpatient or inpatient treatment setting. Both settings are commonly used in the treatment of depression and are appropriate for the purpose of the study. The inpatient and outpatient setting in this study includes a frequent visit schedule (weekly). As the outpatient setting may increase the risk of subject suicidality, weekly collections of information about the suicidality risk are implemented.

For the primary objective, the efficacy will be determined using the MADRS (Montgomery and Asberg 1979) which is a standard for the evaluation of a major depressive episode.

4.2 Rationale for dose/regimen and duration of treatment

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4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The use of placebo saline solution is to provide a comparison group for an unbiased collection and assessment of safety and tolerability data.

Ketamine is included primarily for assay sensitivity and for comparison of side effects. Ketamine is known to be effective with large effect sizes for severe depressive episodes, and it also has high rates of dissociative side effects in 20-30% of subjects, often of moderate to marked severity. It also can cause manic episodes, mixed states, and suicidal or aggressive reactions in a small minority of persons. A single subanesthetic dose of intravenous ketamine consistently decreases symptoms of depression in subjects with treatment-resistant depression in a rapid (within hours), robust (across many symptoms of depression) and relatively sustained (typically, 7–14 days) manner (Berman et al 2000; Cusin et al 2017). Repeated doses (six infusions over the course of several weeks) have shown promise from an efficacy and safety standpoint (Aan het Rot et al 2010). The efficacy of two times versus three times a week intravenous ketamine in subjects with treatment-resistant depression in sustaining the initial antidepressant effects was evaluated. Both doses (0.5 and 0.75 mg/kg) were significantly superior to placebo in treating depression symptoms and the transient dissociative side effects attenuated with repeat dosing (Singh et al 2016). One study examined the benefits of a fixed course of 4 once-weekly ketamine sessions (0.5 mg/kg IV) as continuation phase treatment in 5 patients who had remitted after acute phase treatment. All 5 patients maintained improvement during the continuation phase (Krystal et al 1994).

To limit any dissociative and psychomimetic side effects, the limiting dose for Ketamine infusion is at 40 mg/infusion for patients over 80 kg.

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

There is no expected benefit for subjects participating in the study. However, in instances of documented TRD, participants may benefit from receiving effective antidepressant therapy to treat the MDD.

The risks of participating in the study include those identified in the clinical studies with MIJ821, those associated with IV infusion and those associated with blood sampling. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria, specific procedures done by qualified personnel, study stopping rules as well as close clinical monitoring.

Subjects will be observed for 2-4 hours (i.e. a minimum of 2 hours) after the start of infusion. If they have no dissociative symptoms and no suicidal symptoms after the observation period, they can leave the clinical treatment setting. If investigators judge that subjects have any dissociative symptoms, subjects will be monitored in the clinic until the dissociative symptoms resolve and/or extended stay overnight, or longer based on investigator judgment. If suicidal symptoms are present to a moderate to severe degree, either based on rating scales or investigator judgment, and such symptoms persist throughout the above 2-4 hours monitoring period, investigators may consider extending stay of subjects at least overnight. If suicidal symptoms are mild, either based on rating scales or investigator judgment, the investigator's judgment can be used to allow the subject to leave the clinical setting, but in that case arrangements should be made such that family members or friends are present with the subject for at least 24 hours. If such arrangements cannot be made, the subject may have extended stay at least overnight. If needed, an additional overnight stay beyond the first infusion's baseline and V101 is permissible.

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, he/she should not be entered or continue in the study.

Sexually active males must be informed of the requirement to wear a condom for the following reasons:

- Prevent pregnancy in a female partner AND
- Present delivery of investigational drug via seminal fluid to their partner as study treatment may involve unknown risks to the fetus if pregnancy were to occur.

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Given that MIJ821 may impair the mental or physical abilities required for the performance of dangerous potential tasks such as driving a car or operating machinery, subjects should be advised about these potential risks. If the subject is feeling drunk or dizzy or if he/she experiences visual disturbances, hallucinations, or euphoric mood, then the subjects should not drive, use machines or perform any other tasks that require his/her attention and good coordination. In that case, the subject should be hospitalized until resolution of these events. These judgments will be made by the investigators, not the subjects.

In general, hypersensitivity or infusion reaction can manifest with itching, flushing, headache, nausea, vomiting, hypotension, urticaria, bronchospasm, or angioedema. In the event of a hypersensitivity reaction, stop the infusion immediately.

Subjects participating to the MIJ821X2201 study will be provided with a subject information card that they would carry with them at all time and as long as they are treated with MIJ821 or ketamine. This card will warn of potential interaction with CYP3A4, CYP2B6, CYP2C8, CYP2C19, or CYP2D6 inducers or inhibitors and should be presented to every physician/healthcare provider the subject may consult to inform them about potential drug interactions. It is also important that the subject is asked to contact his/her study doctor to inform him/her of his/her status as well as to discuss any treatment recommendations. As a general precaution with all investigational drugs, sites should have the capacity of managing acute hypersensitivity reactions (or similar emergency situations) or be prepared to transfer the subject urgently, should these reactions emerge.

Benefits of ketamine have been shown for rapid improvement of depressive symptoms within 1-2 days, which persists up to 3-4 weeks after one dose. This improvement has been shown mainly with intravenous infusion of 0.5 mg/kg ketamine over 40 minutes (Katalinic et al 2013). Two open-studies (Price et al 2009, Thakurta et al 2012) also have suggested that ketamine may be an appropriate treatment to rapidly reduce acute suicide risk in depressed patients. Benefits have been shown also recently with intranasal administration of esketamine. These benefits occur for acute depressive symptoms, and have not been studied or proven for long-term or maintenance administration. The amount of benefit seen acutely meets or exceeds the effect sizes seen with standard antidepressants. Some studies report such benefit in treatment-resistant depression, with patients who have failed multiple prior antidepressant trials. Such benefit has been seen with both bipolar and unipolar depression.

Most of the research conducted using subanaesthetic doses of ketamine has shown psychotomimetic and neuropsychological adverse effects: general psychiatric symptoms, agitation, dissociative symptoms and manic symptoms. These effects have mostly been restricted to the time of administration, disappearing completely by 60 minutes afterward. Other adverse events experienced by patients include feelings of intoxication and lowered inhibitions, confusions, decreased concentration and perceptual disturbances. Most of these

impairments were only apparent during the infusions, and none persisted longer than 2 hours after the beginning of the infusions.

There have been not many significant physical adverse event reported in studies of low-dose ketamine (used as an antidepressant) to date. Some studies have reported a variety of non-permanent physical effects such as light-headedness, headache, nausea, diplopia, drowsiness and dizziness. These symptoms tend to be benign and again limited to the period of the infusion or for a short time following.

Depression trials investigating subanaesthetic doses of ketamine consistently report transient elevations in blood pressure and heart rate during the period of infusion and for up to 80 minutes after dosing.

There have been a number of case reports that have linked repeated ketamine use to urinary tract problems. These cases have mainly been reported in the context of recreational ketamine abuse (where use is chronic, doses are high, and comorbidity with other substance use is common).

Finally, there are concerns about the potential for dependence through long-term or repetitive ketamine use. However, low-dose usage in a medical setting is less likely to produce tolerance (Katalinic et al 2013).

The above risks will be minimized in this trial by clinical observation during and for 2-4 hours (i.e. a minimum of 2 hours) after the start of infusion period, as well as extended stay if needed based on clinical judgment at any point during the study. If severe dissociative, psychotic, suicidal, or agitated symptoms emerge, clinician-researchers will hospitalize research subjects until those clinical adverse events are resolved. If they persist, or based on clinician-researcher judgment or patient preference, those subjects can be dropped from the study as well at any time. Certain benzodiazepines, specifically lorazepam or alprazolam (as authorized by country), administration also is allowed in the study, within dosage limitations, to manage such possible agitation-related effects of ketamine.

The risk of collecting blood may include fainting, pain and/or bruising: rarely, these may be a small blood clot or infection at the site of the needle puncture. The risks with an IV infusion may include pain, swelling, redness or infection at the injection site. The risk is mitigated by selecting professional staff from the clinic experienced in making this type of infusion.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 6 weeks, from each subject as part of the study (representing a total of around 220 ml). Additional samples may be required for safety monitoring.

Timing of blood sample collection is outlined in the Assessment schedule.

A summary blood log is provided in the SOM. Instructions for all sample collection, processing, storage and shipment information are also available in the SOM and central laboratory manual.

5 Population

Approximately 66 subjects (66 completers for the primary endpoint) diagnosed with treatment-resistant depression will be randomized to:

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In the USA, no ketamine arm will be included.

It will be competitive recruitment per region.

The investigator or designee must ensure that all subjects being considered for the study meet the following eligibility criteria.

Subject selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any of the entry criterion excludes a subject from enrollment into the study.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Male and female subjects, 18 to 65 years of age (inclusive) at screening.
3. SCID-based DSM-5 defined major depressive episode at the time of screening.
4. Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥ 24 at screening and baseline.
5. Failure to respond to two or more antidepressant treatments, where two failed treatments are of two different antidepressants and at least one of which is in the current depressive episode, with adequate dose and duration (≥ 8 weeks duration, doses defined per agent), as identified by the Maudsley Treatment Inventory, and prior psychiatric history, assessed by the investigator, and further documented by medical records and/or third party report (family, friends, clinician-treaters) where available
6. If patients are taking any type of psychotropic drugs, a stable dose of psychotropic drugs at screening is defined as no changes in dose or type of antidepressants, antipsychotics, or mood stabilizers for at least 2 weeks prior to screening, if applicable.
7. No new antidepressant initiated 4 weeks or less before baseline, and 6 weeks or less before baseline if subject is initiated on fluoxetine

8. At least one prior clinical depressive episode (recurrent major depressive disorder), as identified by prior psychiatric history assessed by the investigator, and further documented by medical records and third party report (family, friends, clinician-treaters) where available.
9. Able to communicate well, and to understand and comply with study requirements

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Any current diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorder at screening.
2. Current alcohol or substance use disorder (including marijuana and prescribed amphetamine)) meeting DSM-5 criteria, within the past month at baseline. Nicotine and caffeine use disorders will not be considered as exclusionary.
3. Prior suicidality caused by or associated with ketamine, as identified by prior psychiatric history assessed by the investigator, and augmented by medical records and third party report (family, friends, clinician-treaters) where available.
4. Acute serious and/or imminent suicidal ideation and/or intent within the prior 2 weeks, or any suicide attempt within the prior 4 weeks at screening. Mild to moderate suicidal ideation, using the Sheehan Suicidal Ideation Scale and not meeting the above definition, is not an exclusion criterion.
5. Use of other investigational drugs within 30 days or 5 half-lives of randomization, whichever was longer; or longer if required by local regulations at baseline.
6. Current pregnancy or lactation.
7. Positive HIV, Hepatitis B or C test.
8. Resting QTcF ≥450 msec (male) or ≥460 msec (female) at pre-treatment baseline
9. History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in this study.
10. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within 3 years of screening, regardless of whether there is evidence of local recurrence or metastases.
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for 1 week after stopping of investigational drug. Highly effective contraception methods include:
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking study treatment.

If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. Refer to Section 8.4.3 (Pregnancy and Assessments of Fertility).

12. Sexually active males unwilling to use a condom during intercourse while taking investigational drug and for 1 week after stopping study treatment. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of the investigational drug via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above.
13. History of hypersensitivity to any of the study treatments or excipients or to drugs similar to chemical classes that affect NMDA receptor.
14. Current diagnosis of borderline personality disorder or antisocial personality disorder, based on DSM-5 criteria.
15. Current acute depressive episode lasting longer than two years continuously, defined as no two week or longer period where depressive symptoms are subsyndromal in severity for a full DSM-5 acute major depressive episode.
16. Considered by the investigator, for any other reason, to be an unsuitable candidate for the study.

General Note: In the case where a safety assessment at screening is outside of the range specified above, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject is excluded from the study.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM and the Pharmacy Manual.

6.1.1 Investigational and control drugs

Table 6-1 Overview of study medication

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Packaging	Provided by
MIJ821 20 mg	Powder for solution for infusion	Intravenous use	Open label bulk supply; vials	Novartis
Placebo	0.9% sodium chloride	Intravenous use	Open label; infusion bag	Novartis (EU) or locally by site (US)
Ketamine 0.5 mg/kg limiting dose at 40 mg/infusion for patients over 80 kg	Concentrate for solution for infusion Solution for injection	Intravenous use	Open label; vials	Novartis

The investigational drug MIJ821 will be available as lyophilisate in dose strength of 20 mg per vial. MIJ821 will be packed and labeled under responsibility of Novartis and will be supplied to the investigator sites. MIJ821 preparation instructions will be provided in the Pharmacy Manual.

The active comparator, ketamine will be provided to the investigators by Novartis and the placebo (saline 0.9% sodium chloride) will be sourced by Novartis (EU) or locally by site (US).

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM.

6.1.2 Additional study treatments

No additional treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Subjects will be assigned at the baseline to one of the following 6-treatment arms in the European countries (5-treatment arms in the USA) in a ratio defined on the Section 5.

6.2 Other treatment(s)

No additional treatment beyond investigational drug, comparator and placebo are included in this trial.

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies CRF.

The risk of clinical drug-drug interaction of MIJ821 and concomitant medications has not been completely assessed. Based on non-clinical investigations and preliminary, qualitative risk estimation, appropriate caution is recommended for MIJ821 concomitantly given with inhibitors/inducers of CYP2D6, CYP2C19, and CYP2C8 especially CYP2D6 inhibitors like e.g. bupropion, fluoxetine, paroxetine, and duloxetine.

To minimize the risk of clinical drug-drug interaction, the following has to be followed:

- If patients are treated with an infusion during the morning hours, they should take their evening concomitant medications the prior night, but they should not take their morning concomitant medications until at least two hours after the end of the infusion.
- If patients are treated with an infusion from 12 noon onwards, again they should not take their morning concomitant medications until at least two hours after the end of the infusion.

Each concomitant drug must be individually assessed against all inclusion criteria. If in doubt the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

All allowed concomitant baseline psychotropic medications must remain unchanged throughout the study. No new psychotropic drug should be started after baseline. All non-psychotropic medications should be changed as little as possible. Certain benzodiazepines, specifically lorazepam or alprazolam (as authorized by country), will be allowed for use on an as needed basis for emergency agitation/anxiety, during infusion, in the morning before infusion (details in Section 6.2.1) and 2 hours post-infusion, not to exceed 2 mg in a 24 hour period. Such lorazepam or alprazolam use will be documented as concomitant medication(s).

6.2.2 Prohibited medication

There are no prohibited medications. Agents that are inhibitors/inducers of CYP2D6, CYP2C19, and CYP2C8 will be allowed but will be monitored carefully by the medical monitor and pharmacokinetics will be examined carefully. Also administration of MIJ821 and such CPY450 agents will not be given at the same time range.

6.2.3 Restriction for study subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

6.2.3.1 Dietary restrictions and smoking

No dietary or smoking restrictions in this study.

6.2.3.2 Other restrictions

If the subject is feeling drunk or dizzy or if he/she experiences visual disturbances, hallucinations, or euphoric mood, then the subject should not drive, use machines or perform any other tasks that require his/her attention and good coordination.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

6.3.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider, or by a delegate under Novartis supervision, using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

Randomization will be stratified by region, US and European countries.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site Staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.6.3).

Drug product will be supplied in bulk, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. After blinded investigator or his/her delegate performs the randomization in NIRT system, the unblinded pharmacist will log into the NIRT system and see the treatment arm assigned to the randomized subject. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor Staff

The following unblinded sponsor roles are required for this study:

- Unblinded field monitor(s)
- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample analyst(s) (PK)

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors will be unblinded through unblinded user access to the NIRT system and review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual subjects.

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with treatment assignment directly, but may be unblinded through communication of drug re-supply needs via the unblinded site pharmacists.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the treatment assignments for interim analyses (if any) and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-2. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep treatment allocation and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-2 Blinding and unblinding plan

Role	Time or Event		
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)
Subjects	B	B	UI
Site staff	B	B	UI
Unblinded site staff e.g. pharmacy staff	B	UI	UI
Drug Supply and Randomization Office	UI	UI	UI
Unblinded sponsor staff e.g. for study treatment re-supply, unblinded monitor(s), sample analysts (Bioanalytical study monitor and bioanalytical lab personnel), Translational Medical expert, study leads, Clinical Trial Associate	B	UI	UI
Unblinded Pharmacovigilance sponsor staff	B	B	UI
Statistician/statistical programmer/ data analysts (e.g. Commercially Confidential Information PK)	B	B	UI
Independent committees used for assessing interim results, if required (e.g. DMC)	NA	NA	NA
All other sponsor staff not identified above (trial team, project team, management & decision board, support functions)	B	B	UI

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UI: Allowed to be unblinded on individual subject level

B: Remains blinded

NA: Not applicable to this study

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions in infusions are not permitted. If a subject misses a weekly dose, Novartis medical monitor must be contacted to determine if this subject can remain on study and continue with subsequent weekly infusions.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The treatment will be administered at the site. The investigator must ensure compliance by instructing the study personnel to deliver the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. Compliance will be assessed by the investigator and/or study personnel at each visit by ensuring that the full infusion was effectively delivered to the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with MIJ821, as detailed in the pharmacokinetics Section 8.5.2.

Please refer to the SOM and Pharmacy Manual for further details.

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events.

Medication used to treat AEs must be recorded on the Concomitant Medications/Significant non-drug therapies CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the Novartis IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the NIRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

After an emergency code break, the subject cannot continue the study.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under Section 6.1.1 (Investigational and control drugs).

For the drug preparation prior to administration, please refer to the Pharmacy Manual.

A unique medication number is printed on the study medication label.

MIJ821 will be administered to the subject via the following route of administration: i.v. The administration of the study treatment will occur at the study site. See the SOM and Pharmacy Manual for further details.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Refer to the SOM for a complete list of ICFs included in this study.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment Schedule

Epoch	Screening		Treatment																				
Visit Name	Screening	Baseline	Treatment																	Follow up		End of Study
Visit Numbers[1]	1	2	101				102	103[12]	104		105		106		107			108		201	202	299
Days	-28 to -2	-1 to 1	1				2	3	8		15		22		29			36		43	57	71
Time (post-dose)	-	-	0h[2]	CCI	1h	4h	24h	48h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	0.67h[3]	2-4h	0h[2]	2-4h	-	-	-
Informed consent	X																					
Inclusion / Exclusion criteria	X	X																				

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Medical history/current medical conditions	X																					
Alcohol Test and Drug Screen	S[5]		S[5]																			
Hepatitis and HIV Screen	S[5]																					
Pregnancy and assessments of fertility[6]	X[7]	X[8]													X[8]						X[8]	X[7]
Demography	X																					
Body Height	X																					
Body Weight	X																			X		
Physical Examination	S[5]																			S		
Vital signs and body measurements	X	X	X		X	X[13]	X	X	X	X[13]	X	X[13]	X	X[13]	X	X	X[13]	X	X[13]	X		

Epoch	Screening		Treatment																				
Visit Name	Screening	Baseline	Treatment																		Follow up		End of Study
Visit Numbers[1]	1	2	101				102	103[12]	104		105		106		107			108			201	202	299
Days	-28 to -2	-1 to 1	1				2	3	8		15		22		29			36			43	57	71
Time (post-dose)	-	-	0h[2]	CCI	1h	4h	24h	48h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	0.67h[3]	2-4h	0h[2]	2-4h		-	-	-
Electrocardiogram (ECG)	X		X[9]						X				X								X		
Hematology	X		X						X				X								X		
Clinical Chemistry	X		X						X				X								X		
Urinalysis	X		X				X																

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PK blood collection			X	X		X	X[11]	X							X	X							
Dose administration (40 min)			X						X		X		X		X			X					
Structured Clinical Interview for DSM-5	S[5]																						

Epoch	Screening		Treatment																				
Visit Name	Screening	Baseline	Treatment																	Follow up		End of Study	
Visit Numbers[1]	1	2	101				102	103[12]	104		105		106		107			108		201	202	299	
Days	-28 to -2	-1 to 1	1				2	3	8		15		22		29			36		43	57	71	
Time (post-dose)	-	-	0h[2]	CCI	1h	4h	24h	48h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	0.67h[3]	2-4h	0h[2]	2-4h	-	-	-	
Maudsley Treatment Inventory	X																						
Sydney Melancholia Prototype Index	X																						
Melancholia and Mixed Depression Diagnostic Checklist	X																						
Concomitant therapies	X	X	X[9]				X	X	X		X		X		X			X		X	X	X	
Montgomery-Asberg Depression Rating Scale	X	X	X[9]		X		X	X	X		X		X		X			X		X	X	X	
Bech Rafaelsen Melancholia Scale		X	X[9]		X		X	X	X		X		X		X			X		X	X	X	
CORE Melancholia Scale		X	X[9]		X		X	X	X		X		X		X			X		X	X	X	
Young Mania Rating Scale		X	X[9]		X		X		X		X		X		X			X		X	X	X	
Clinical Global Impression of Severity		X	X[9]		X		X	X	X		X		X		X			X		X	X	X	
Clinical Global Impression of Improvement							X	X	X		X		X		X			X		X	X	X	

Epoch	Screening		Treatment																				
Visit Name	Screening	Baseline	Treatment																		Follow up		End of Study
Visit Numbers[1]	1	2	101				102	103[12]	104		105		106		107			108			201	202	299
Days	-28 to -2	-1 to 1	1				2	3	8		15		22		29			36			43	57	71
Time (post-dose)	-	-	0h[2]	CCI	1h	4h	24h	48h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	0.67h[3]	2-4h	0h[2]	2-4h		-	-	-
Clinician Administered Dissociative States Scale		X	X[9]		X		X	X	X		X		X		X			X			X	X	X
Dissociative Experiences Scale (DES)		X	X[9]		X	X	X	X	X		X		X		X			X			X	X	X
Generic Assessment of Side Effects in Clinical Trials (patient self-rating)		X	X[9]		X		X	X	X		X		X		X			X			X	X	X
Hamilton Anxiety Rating Scale		X											X								X		
Koukopoulos Mixed Depression Rating Scale		X	X[9]		X		X	X	X		X		X		X			X			X	X	X
Sheehan Suicidality Scale	X	X	X[9]		X		X	X	X		X		X		X			X			X	X	X
Adverse Events	X	X	X[9]	X	X		X	X	X		X		X		X			X			X	X	X
Serious Adverse Events	X	X	X[9]	X	X		X	X	X		X		X		X			X			X	X	X

Epoch	Screening		Treatment																				
Visit Name	Screening	Baseline	Treatment																		Follow up		End of Study
Visit Numbers[1]	1	2	101				102	103[12]	104		105		106		107				108		201	202	299
Days	-28 to -2	-1 to 1	1				2	3	8		15		22		29				36		43	57	71
Time (post-dose)	-	-	0h[2]	CCI	1h	4h	24h	48h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	2-4h	0h[2]	0.67h[3]	2-4h	0h[2]	2-4h		-	-	-
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Study completion information																				X			
Comments	X	X	X	X			X	X	X		X		X		X				X	X	X	X	X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Visit structure given for internal programming purpose only
[2] Unless specified in the Assessment Schedule, all assessments are to be done before start of infusion

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[5] S = assessment to be recorded on source documentation only and will not be entered into the eCRF. If drug screen result is positive but does not meet DSM-5 criteria for substance use disorder, the subject can be enrolled.
[6] Additional pregnancy testing may be performed at each visit to meet local requirements.
[7] Serum pregnancy test
[8] Urine pregnancy test
[9] Not to be repeated if baseline visit and V101 are conducted on the same day.

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[11] 24 hours after start of the first infusion
[12] V103 48 hours is an optional visit, however if V103 is conducted, all assessments should be completed.
[13] Assessments to be conducted once between 2 and 4 hours, and at 6 hours if there is an extended stay.

8.1 Screening

It is permissible to re-screen a subject if he/she fails initial screening. However, each case must be discussed and agreed with the sponsor on a case-by-case basis. There is no time frame for performing the re-screening tests.

In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

If the subject is re-screened, he/she needs to sign again a new informed consent.

Information on what data must be collected for screening failures and further information on re-screening is outlined in the SOM.

8.1.1 Information to be collected on screening failures

Information on what data should be collected for screening failures is outlined in the SOM.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the SOM.

Hepatitis and HIV test will be performed for samples collected at screening

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

8.3.1 Montgomery Asberg Depression Rating Scale

The Montgomery Åsberg Depression Rating Scale (MADRS), is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment: the test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts and suicidal thoughts (Khan et al 2002). The test exhibits high inter-rater reliability. The typical recall period for the MADRS is 7 days.

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8.3.4 Appropriateness of efficacy assessments

The Montgomery Åsberg Depression Rating Scale (MADRS) now is the standard scale used for registration studies of depression. It is relatively quick to administer (20 to 30 minutes), does not focus predominately on the somatic symptoms of depression, but rather addresses core mood symptoms such as sadness, tension, lassitude, pessimistic thoughts, and suicidal thoughts. The MADRS is more sensitive to change from treatment effects over time than the Hamilton Depression Rating Scale (HDRS), and has replaced the latter as the gold standard registration scale for depression. All secondary scales are psychometrically validated and reliable as measures of subtypes or symptom features of depressive states. They are being used to explore possible subtype effects or associated symptom changes to clarify which aspects of treatment-resistant depression may improve more or less with the interventions given. Those results will be descriptive and used for hypothesis generation for future studies.

8.4 Safety / Tolerability

Safety assessments are specified below with the Assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1.1.

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.
Vital sign	Vital signs include temperature, BP and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

The methods, assessments, specification, and recording for each assessment will be detailed in the SOM.

8.4.1 Laboratory evaluations

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Clinically significant abnormalities must be recorded on the relevant section of the medical history / eCRF page as appropriate.

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

In the case where a laboratory range is not specified by the protocol, but is outside the reference range for the laboratory at screening, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met.

Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Table 8-2 Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured.
Chemistry	Albumin, alkaline phosphatase, total bilirubin, bicarbonate/carbon dioxide (CO2), calcium, cholesterol, chloride, creatinine, creatinine kinase (CK), GGT, glucose, lactic dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, blood urea nitrogen (BUN) uric acid. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. Thyroid Stimulating Hormone (TSH) level will be analyzed as well. In case of abnormal TSH value, additional evaluation will be performed (triiodothyronine [T3] and thryroxine [T4]).
Urinalysis	A midstream urine sample (approximately 30 mL) will be obtained from subjects with no urinary catheters, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. A semi-quantitative “dipstick” evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood. If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

8.4.2 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the SOM.

- PR interval, QRS duration, heart rate, RR interval, QT interval, QTc.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

As applicable, QTcF and QTcB may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the baseline visit to assess eligibility. See the SOM for additional details.

Clinical significant abnormalities must be reported in the AE CRF.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner while taking investigational drug and for 1 week after stopping study treatment. In addition, male participants should not donate sperm for the time period specified above.

Pregnancy

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment schedule (Table 8-1), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements. A positive urine pregnancy test requires immediate halt of study treatment until serum β-hCG is performed and found to be negative.

Refer to Section 10.1.4 for details on Reporting Pregnancy.

Assessments of fertility

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source, if available. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required for any female subject, regardless of reported reproductive/menopausal status at screening.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Clinical Global Impression

The Clinical Global Impression (CGI) is a 3 item observer-rated scale which measures the severity of symptoms, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders (Guy 1976). CGI provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. CGI is rated by an experienced clinician who is familiar with the disease under study and the likely progression of treatment. The CGI is rated without regard to the clinician's belief that any clinical changes are or are not due to medication and without consideration of the etiology of the symptoms.

For the study purpose 2 items will be used: the CGI-Severity, which rates illness severity, and the CGI-Improvement, which rates change from the initiation of treatment. The CGI-Severity is rated at all visit except the screening, and the CGI- Improvement at V102 and all following visits.

Clinical-Administered Dissociative States Scale

The Clinical-Administered Dissociative States Scale (CADSS) (Bremner et al 1998) is a questionnaire that assesses dissociative effects.

Each item is scored from 0 to 4 and individual scores are to be summed to obtain a total score ranging from a minimum of 0 to a maximum of 80. The trained staff administering the scale will also note their subjective interpretation of the subject's mental status and overall wellbeing, and whether any findings could be related to study drug.

The CADSS will be administered at all visits except the screening.

Dissociative Experiences Scale

The Dissociative Experiences Scale (DES) (Bernstein and Putnam 1986) consists of twenty-eight questions about experiences the subject has experienced in his/her daily life. The subject determines to what degree he/she has been facing the situation by selecting a percentage from 0% (never) to 100% (always), with 5% increments in between.

The DES will be administered at all visits except the screening.

Young Mania Rating Scale

The Young Mania Rating Scale (Young et al 1978) has 11 items and is based on the patient's subjective report of his/her clinical condition over the previous 48 hours. Additional information is based on the clinical observation made during the clinical interview.

There are 4 items that are scored from 0 to 8 (irritability, speech, thought content, and disruptive/aggressive behavior) and the remaining items are scored from 0 to 4.

The Young Mania Rating Scale will be administered at all visits except screening and V103.

Bech Rafaelsen Melancholia Scale

Depression scales are used primarily to measure changes, for example, to evaluate the efficacy of treatment with antidepressants. The Bech-Rafaelsen Melancholia Scale (BRMS) is a frequently used clinician rating scale to assess the severity of depression over the past 3 days (Bech et al 1975). Each of the 11 BRMS items is operationally defined on a five-point scale (0-4); hence, the total score ranges from 0 to 44, higher scores indicating greater severity of depression.

The BRMS will be administered at all visits except screening.

CORE Melancholia Scale

This scale is an 18 item scale, with a 6 item component capturing cognitive impairment and two motoric scales capturing psychomotor retardation (7 items) and psychomotor agitation (5 items). A cut-off score of 8 or more has been shown to differentiate melancholic from non-melancholic depression, with higher scores representing a greater probability of melancholic depression. (Parker and McCraw 2017).

The CORE will be administered at all visits except screening.

Maudsley Treatment Inventory

The Maudsley Treatment Inventory (MTI) is a semi-structured instrument that was developed to document psychotropic medications and physical therapies used in the treatment of depression (Fekadu et al 2018). The inventory is primarily designed for use in the current episode, for which treatment resistance is being rated for. However, the MTI may also be used for rating treatment resistance for multiple episodes.

The MTI will be administered at screening.

Generic Assessment of Side effects in Clinical Trials

The Generic Assessment of Side Effects (GASE) in Clinical Trials (Rief et al 2009) is an instrument to assess side effects in clinical trials. The GASE is a self-rating scale consisting of 36 items organized by body parts. The information collected is based on the past week. GASE takes 5 minutes on average to be completed.

The GASE will be administered at all visits except screening.

Structured Clinical Interview for DSM-5

The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide for making the major DSM-5 diagnoses. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. The version used for this trial is the Clinician Version SCID-5-CV.The Structured Clinical Interview for DSM-5-Clinician Version guides the clinician step-by-step through the DSM-5 diagnostic process. Interview questions are provided conveniently along each corresponding DSM-5

criterion, which aids in rating each as either present or absent. The SCID-5-CV covers the DSM-5 diagnoses most commonly seen in clinical settings: depressive and bipolar disorders, schizophrenia spectrum and other psychotic disorders, substance use disorders, anxiety disorders (panic disorder, agoraphobia, social anxiety disorder, generalized anxiety disorder), obsessive-compulsive disorder, posttraumatic stress disorder, attention-deficit/hyperactivity disorder, and adjustment disorder. It also screens for 17 additional DSM-5 disorders.

The SCID-5-CV will be administered at screening.

Sydney Melancholia Prototype Index

With Sydney Melancholia Prototype Index (SMPI), this diagnostic index is a one page assessment of two basic prototypes of depression, melancholic versus non-melancholic, each with 12 descriptive items. Clinicians are asked to check a box for any item which fits the patients description, and then to provide an overall rating about whether the patient more closely approximates one or the other of the two basic prototypes. (Parker and McCraw 2013).

The SMPI will be administered at screening.

Melancholia and Mixed Depression Diagnostic Checklist

With Melancholia and Mixed Depression Diagnostic Checklist (MMDC), clinicians will be asked to fill out a 1 ½ page form which provides a checklist for diagnostic criteria for mixed depression according to two different definitions, and a checklist for melancholia. The first mixed depression checklist, created by Koukopoulos, has 8 criteria, which are marked as present or absent. If 3 or more criteria are marked present, then mixed depression would be diagnosed. The second mixed depression checklist, created by Angst, lists the 7 criteria for mania from DSM-5, which are marked as present or absent. If 3 or more criteria are marked present, excluding any duration criterion, then mixed depression would be diagnosed. The melancholia checklist, created by Ghaemi for this study, has 4 criteria, which are marked as present or absent. If 3 or more criteria are marked present, then melancholia would be diagnosed. All of the above checklists occur in the presence of a DSM-5 defined major depressive episode, which is an inclusion criterion for this study, and would have been determined beforehand by application of the SCID above.

The MMDC will be administered at screening.

Hamilton Anxiety Scale

The Hamilton Anxiety Rating Scale (HAM-A) measures psychic anxiety and somatic anxiety symptoms based on a clinical assessment and patient interview. The scale has 14 items, with each item rated from 0-4, ranging from not present to very severe. A maximum score of 56 indicates the most severe case. (Hamilton 1959).

The HAM-A will be administered at baseline, V106 and V201.

Koukopoulos Mixed Depression Rating Scale

The Koukopoulos Mixed Depression Rating Scale (KMDRS) assesses the excitatory or mixed nature in patients suffering from a Major Depressive Episode (MDE) as defined by DSM-5 criteria. This scale is meant to be used in conjunction with another scale that assess typical depression and anxiety symptoms. The scale contains 14 items to be evaluated by clinical assessment and patient interview on symptoms potentially experienced over the past week. Overall score increases with severity of symptoms and has a maximum score of 51. (Sani et al 2018).

The KMDRS will be administered at all visits except screening.

8.5.2 Pharmacokinetics

Pharmacokinetic (PK) samples will be collected at the time points defined in the Assessment schedule (Table 8-1). Follow instructions outlined in the SOM and in the Bioanalytical study specification regarding sample collection, numbering, processing and shipment.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

PK samples should be collected in all patients to avoid unblinding. Only the samples from patients treated with MIJ821 will be analyzed

Pharmacokinetic analytical method(s)

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Pharmacokinetic parameters

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Commercially Confidential Information

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject's decision
- Pregnancy
- Any situation in which study participation might result in a safety risk to the subject
- CTC-AE Grade 3 or higher adverse event unless it can be conclusively shown that AE is not related to study treatment.
- Severe hypersensitivity reaction such as anaphylaxis
- Any protocol deviation that results in a significant risk to subject safety
- Adverse events, abnormal laboratory values or abnormal test result that indicate a safety risk to the subject

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject’s premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2). Where possible, subjects should return for V299 and complete the assessments indicated in the Assessment schedule for this visit. If subjects fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 9.1.3. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

The investigator must also contact the IRT to register the subject’s discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.1.1 Replacement policy

Subjects who are withdrawn from the study for reasons other than safety, the decision to replace them by an equal number of newly enrolled subjects will be taken by the Sponsor.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore

and

- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Study stopping rules

The study will be stopped, and no further enrollment will take place pending a full safety review, if any of the following criteria are met:

- At least 5 subjects in any single treatment arm experience an AE of Grade 3 or higher according to the CTC-AE V5.0 and is potentially related to study treatment
- Two or more treatment-emergent SAEs, except those that are clearly and incontrovertibly due to extraneous causes;
- The Sponsor considers that the number and/or severity of AEs justify putting the study on hold.

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their study completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision (e.g. each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

All randomized and/or treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and SOM. Documentation of attempts to contact the subject should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade (version 5.0 or higher). A copy of the CTCAE grading will be provided separately in the SOM.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

2. its relationship to the study treatment and other investigational treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. its outcome.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. Continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

Follow the instructions found in the SOM for data capture methodology regarding AE collection for subjects that fail screening.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Event common in the subject population under study: during studies, the unblinding of single SAEs, that are relatively common in the subject population under study, for SUSAR reporting, often does not increase the understanding of safety, and can damage the integrity of the blinded nature and analysis of a study. The study protocol may then contain a "Table of AEs Commonly Seen in the Subject Population" that are still captured by the investigator as AEs and SAEs in the CRF and reported to Novartis for the SAEs, but they would not be unblinded

during the course of the study, even if considered "related" to study treatment by the reporting investigator, nor reported on an expedited basis to regulatory authorities.

IMPORTANT: To comply with regulations, all suspected, unexpected, serious adverse reactions (SUSARs) occurring in a clinical trial must be reported in an expedited timeframe (7 or 15 days) to competent authorities.

Consider the following 2 categories to determine SAE reporting timeframes:

1. Screen Failures (e.g. a subject who is screened but is not treated or randomized): SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.
2. Randomized OR Treated Subjects: SAEs collected between time subject signs ICF until 30 days after the subject has discontinued or stopped study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The newborns will be followed up for 3 months after delivery.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 10.1.1 and Section 10.1.2, respectively.

10.2 Additional Safety Monitoring

Not applicable.

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 16-1 in Appendix 1 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unplanned local laboratory CRF
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

Refer to the SOM for additional details.

10.2.2 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR new onset dipstick proteinuria ≥ 3+ OR new onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Renal event findings must be confirmed 24-48 hours after the first assessment.

Every renal laboratory trigger or renal event as defined in Table 16-3 should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.2.

Refer to the SOM for additional details.

10.2.3 Prospective suicidality assessment

The Sheehan Suicidality Tracking Scale is a sensitive psychometric tool to prospectively assess for treatment-emergent suicidal thoughts and behaviors. The Sheehan Suicidality Tracking Scale (Sheehan-STS) is a prospective rating scale that tracks both treatment-emergent suicidal ideation and behaviors. The Sheehan-STS is afourteen-item (up to 22) scale that will be administered by a clinician. Each item in the Sheehan-STS is scored on a 5-point Likert scale

(0=not at all, 1=a little, 2=moderately, 3=very, and 4=extremely). Data from the Sheehan-STS can be analyzed as individual item scores, suicidal ideation subscale score (sum of scores from items 2, 3, and 4, plus score from item 5 if ≤1), suicidal behavior subscale score (sum of scores from items 6, 7a, and 8, plus score from item 5 if >1), and total score.

10.2.4 Data Monitoring Committee

Not required.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using the Novartis Interactive Response Technology (NIRT).

Each occurrence of a code break via NIRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

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11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS and the safety analysis set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

Data for study drug administration and concomitant therapies will be summarized by treatment group.

Total duration of time on study drug and reasons for discontinuation of study drug will be summarized by treatment group.

All available data under safety analysis set will be used for reporting purpose.

12.4 Analysis of the primary endpoint(s)

The primary aim of this study is to determine whether MIJ821 displays clinical efficacy and safety to support further development for treatment-resistant depression.

12.4.1 Definition of primary endpoint(s)

The primary efficacy endpoint is change from baseline in the total MADRS score at 24 h after single dose administration. The primary analysis will be performed on the ITT set. In addition, a similar analysis will be performed on the PPS.

The primary efficacy analysis may be performed once the 24-hour outcome data on MADRS score are available from all study participants. These results may help facilitate further planning activities within the MIJ821 program.

12.4.2 Statistical model, hypothesis, and method of analysis

The change from baseline in the total MADRS score at 24 hours after single dose administration will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a group factor and baseline MADRS score as a covariate.

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12.4.3 Handling of missing values/censoring/discontinuations

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No imputation of missing data will be done for the primary analysis approach.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

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Commercially Confidential Information

Supportive analyses

Commercially Confidential Information

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamics endpoint(s)

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12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

Adverse events

All information obtained on AEs will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment emergent AEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term;
- by treatment, primary system organ class, preferred term and maximum severity;
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs leading to discontinuation.

The incidence of psychotomimetic AEs will be tabulated by treatment group, according to severity and relationship to drug.

A subject with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities as well as clinical notable values will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, subject and visit/time; abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Other safety evaluations

Sheehan suicidality scale score data will be listed by treatment, subject and visit/time; abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time as appropriate.

12.5.3 Pharmacokinetics

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12.5.4 PK/PD relationships

Exposure-response analyses will be carried out for relevant endpoints measured in this study.

12.5.5 Patient reported outcomes

Not Applicable.

12.6 Analysis of exploratory endpoints

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12.6.3 Other Exploratory Endpoints

Commercially Confidential Information

12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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12.8.2 Secondary endpoint(s)

Not Applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST < 5 x ULN • 1.5 x ULN < TBL < 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 5 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50 % [+] **OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m²**	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Assess & document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+] Corresponds to KDIGO criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology.

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-4 Renal Event Follow Up

FOLLOW-UP OF RENAL EVENTS

Assess, document and record in CRF

- Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells
- Blood pressure and body weight
- Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid
- Urine output

Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF

Monitor patient regularly (frequency at investigator's discretion) until -

- Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or
- Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.
- Analysis of urine markers in samples collected over the course of the DIN event