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MIJ821

Clinical Trial Protocol CMIJ821B12201 / NCT05454410

A randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, tolerability, and pharmacokinetics of single subcutaneous MIJ821 injection in addition to standard of care in participants with treatment-resistant depression

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List of abbreviations

ACR	Albumin-Creatinine Ratio
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
APA	American Psychiatric Association
APTT	Activated partial thromboplastin time
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
AV	atrioventricular
BDI-II	Beck Depression Inventory II
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CADSS	Clinical-Administered Dissociative States Scale
[redacted]	
CK	creatinine kinase
ClinRO	Clinician Reported Outcomes
cm	centimeters
Cmax	maximum plasma drug concentration
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease
CQA	Clinical Quality Assurance
CR	concentration-response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
[redacted]	[redacted]
DBP	Diastolic Blood Pressure
DBS	Deep brain stimulation
DDE	direct data entry
DDI	drug-drug interaction
DIN	Drug Inducted Nephrotoxicity
[redacted]	
DR	Dose Response
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
[redacted]	

EC	Ethics Committee
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
ED50	the dose at which half of the maximum effect is reached
EDC	Electronic Data Capture
EFD	Embryo-fetal development
EMA	European Medicines Agency
EOS	End-of-study
eSAE	Electronic Serious Adverse Event
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First in Human
FSH	Follicle Stimulating Hormone
fT3	free triiodothyronine
fT4	free thyroxine
FWER	Family-Wise Error Rate
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GLP	Good Laboratory Practices
HBcAg	Hepatitis B core antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
hERG	human Ether-à-go-go-Related Gene
HIV	Human immunodeficiency virus
HV	healthy volunteer
I.E.	Intercurrent Event
i.v.	intravenous
IB	Investigator's Brochure
IC50	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
kg	kilogram(s)
LDH	lactate dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver function test

LLOQ	lower limit of quantification
LoE	Lack of Efficacy
MADRS	Montgomery Asberg Depression Scale
MAOI	Monoamine oxidase inhibitors
MCP	Multiple Comparison Procedures
[redacted]	[redacted]
MDD	Major Depressive Disorder
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
mL	milliliter(s)
MMDC	Melancholia and Mixed Depression Diagnostic
mmHg	millimetre of mercury
MMRM	Mixed-effects Model for Repeated Measures
MoA	mechanism of action
MOAA/S	Modified Observer's Assessment of Alertness and Sedation
msec	millisecond
MTD	Maximum Tolerated Dose
NAM	negative allosteric modulator
ng	nanogram(s)
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
NOAEL	no observed adverse effect level
PCR	Protein-Creatinine Ratio
PD	Pharmacodynamic(s)
PE	physical examination
[redacted]	
PK	Pharmacokinetic(s)
PoC	Proof of Concept
[redacted]	[redacted]
PT	prothrombin time
PT/INR	Prothrombin time/International normalized ratio
QTcF	QT interval corrected by Fridericia's formula
RNA	Ribonucleic Acid
RO	receptor occupancy
SCID-5	Structured Clinical Interview for DSM-V Disorders
S-STS	Sheehan-Suicidality Tracking Scale
s.c.	subcutaneous
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic Blood Pressure
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase

SIGMA	Structured Interview Guide for MADRS
SNRI	Selective Norepinephrine Reuptake Inhibitors
SPRAVATO	esketamine
SSRI	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1/2	Elimination half-life
TBIL	Total Bilirubin
TdP	Torsades de Pointes
TEAE	Treatment-emergent adverse event
Tmax	time to reach maximum plasma concentration
TMS	Transcranial magnetic stimulation
TRD	Treatment-Resistant Depression
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UTI	Urinary Tract Infection
VNS	Vagus nerve stimulation
WBC	white blood cell
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of child bearing potential
µM	micromolar

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (IMP) (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
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
Discontinuation from study	Point/time when the participant permanently stops further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 milligrams (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 source data/documents 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 participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications 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
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)

Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
[redacted]	[redacted]
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Pharmacological Standard of Care (SoC)	Pharmacological SoC treatment may include antidepressant, or antidepressant plus augmentation therapy
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant 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
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 02 (04-Nov-2022)

Amendment rationale

The purpose of this protocol amendment is to replace the Mini International Neuropsychiatric Interview (M.I.N.I), used at screening to assess whether the diagnostic criteria have been met, by an equivalent validated instrument: the Structured Clinical Interview for DSM-V Disorders (SCID-5). The M.I.N.I cannot be used in this trial due to difficulties related to copyright license agreement's activities, which cannot be overcome in timely manner.

In order to ensure the appropriate patient population is enrolled in this study, the SCID-5 will be used at screening. The SCID-5 is a widely used structured diagnostic instrument for assessing DSM-5 disorders which was also used in the Proof-of-Concept (CMIJ821X2201) study in participants with Treatment Resistant Depression (TRD).

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- The M.I.N.I was replaced by the SCID-5 in the List of Abbreviations, the Protocol summary, in sections 5.1 Inclusion Criteria, 5.2 Exclusion Criteria, 8.5.1.1 Clinical Reported Outcomes (ClinRO) and in Table 8-1 Assessment Schedule.
- As per exclusion criterion 1, patients who received brain stimulation procedures within one year prior to screening are excluded. Transcranial magnetic stimulation (TMS) has now been added to exclusion criterion 1, section 5.2 Exclusion criteria, as the procedure is currently widely used in some participating countries/clinical sites and the related exclusionary period for brain procedures has been further specified.

Some inconsistencies have also been addressed in the following sections:

- Section 8.5.1.1 Clinician Reported Outcomes (ClinRO)
  It has been clarified that the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) is designed to capture all treatments (failed and successful) used in the current episode, only.
- Section 9.1.3 Lost to follow-up, Section 10.2.1 Liver Safety Monitoring and Section 10.2.3 Cardiac Monitoring
  Any reference to treatment interruption was removed as this is a single dose study.

In addition to the above, correction of broken hyperlinks, minor typographical and formatting errors has been made where needed.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 01 (31-May-2022)

Amendment rationale

The purpose of this protocol amendment is to clarify that the End of-Study (EoS) visit (Day 29) is the last study visit for ensuring safety follow-up and thus a safety follow-up call at Day 31 is not required while taking into consideration the pharmacokinetic profile of MIJ821 (five half-lives of MIJ821). The protocol has the provision to ensure that any related serious adverse events carry on being reported beyond EoS visit unless otherwise specified by local law/regulations.

Furthermore, the protocol is amended to clarify that in case of extended safety monitoring for adverse events on Day 1, between 4 hours and 24 hours post-dose, additional safety tests or measures may be required including but not limited to unscheduled pharmacokinetic (PK) samples.

The recall periods for the Montgomery Asberg Depression Rating Scale (MADRS) [redacted] have been added in order to adequately assess efficacy at the 4 hour-time point on Day 1. In addition the recall period of the MADRS used at screening has been specified: “Last 7 days with euthymic baseline”. The recall period of the Clinician-Administered Dissociative States Scale (CADSS) has also been added. The recall period of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the first study visit has been updated to reflect that this version assesses suicidal ideation and suicidal behavior during the participant's last one year and during a predefined period of one month.

Minor inconsistencies have been addressed in this amendment, and clarifications added where needed.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Protocol Summary
  Section updated for consistency with the main body of the protocol.
- Section 2 Objectives, endpoints and estimands
  The endpoint related to the assessment of the efficacy of MIJ821 on measures of response and remission was updated with the required study days.
- Section 3 Study Design
  Section updated to define End of Study Visit (EoS) as Day 29.
- Section 5.1 Inclusion criteria
  Inclusion criteria 6 wording updated in order to align with protocol text in Section 6.2.1 and Appendix 6 (Antidepressants recommended to be used as background therapy during the study).

- Section 6.4.2 Treatment assignment, randomization
  It has been clarified that the randomization will be stratified by class of current anti-depressant standard of care (Selective Norepinephrine Reuptake Inhibitors (SNRI), Selective Serotonin Reuptake Inhibitors (SSRI) or other anti-depressants or combination of anti-depressants).
- Table 8.1 Assessment Schedule
  Table updated to specify the assessments to be recorded on source documentation only. In addition, Day 31 visit was removed and EoS defined as Day 29. Updates to Section 9 and Section 10 have been made to align with this change.
- Section 8.2 Participant demographics/other baseline characteristics
  Section updated to include the collection of participants' socio-economical and baseline disease characteristic data. This data is part of psychiatric standard of care data collected to characterize the patient's current condition.
- Section 8.3.2 Montgomery Asberg Depression Rating Scale (MADRS), SIGMA version
  Sections updated to include the recall period at baseline and at 4 hour on Day 1.
- Section 8.5.1.1 Clinician Reported Outcomes (ClinRO)
  Sections updated to include a recall period at 4 hour on Day 1 for MADRS [redacted] (to adequately assess efficacy at the 4 hour-timepoint on Day 1) and to update the recall period for C-SSRS at the first study visit.
- Section 8.4.4.1 Clinician-Administered Dissociative States Scale (CADSS)
  The recall period used is "current".
- Section 8.4.4.3 Memory Assessment using orientation questions
  Section updated to clarify that the outcome of this assessment is only captured in the eCRF if amnesia is considered as an AE.
- Section 8.5.2 Pharmacokinetics
  Section updated to clarify that additional PK samples may be collected in case of unscheduled visits for safety monitoring purposes during the time-period from 4 hours to 24 hours post-dose.
- Section 10.2.4 Prospective suicidality assessment
  Section updated to clarify that the "baseline/screening" version of the C-SSRS at the first study visit assesses suicidal ideation and suicidal behavior during the participant's last one year and during a predefined period of one month.
- Section 16.6. Appendix 6.
  The title of the appendix was missing and has been added. In addition, the table was updated with medications that are prohibited only within a time-window before and after study drug injection but can be used as background therapy during the trial. Clarification added in the footer.

In addition to the above, correction of minor typographical errors and clarifications have been made where needed.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CMIJ821B12201
Full Title	A randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, tolerability, and pharmacokinetics of single subcutaneous MIJ821 injection in addition to standard of care in participants with treatment-resistant depression
Brief title	Study of efficacy, safety, tolerability and pharmacokinetics of MIJ821 in participants with treatment- resistant depression (TRD)
Sponsor and Clinical Phase	Novartis Phase IIa
Investigation type	Drug
Study type	Interventional
Purpose	The main purpose of this non-confirmatory study is to evaluate the clinical responses of MIJ821 in participants suffering from TRD treated with a single subcutaneous (s.c.) MIJ821 injection. Furthermore, it is expected that this study will guide the dose selection for future clinical trials with MIJ821 in TRD.
Primary Objective(s)	To assess efficacy of MIJ821 (versus placebo) in TRD after single s.c. injection. The primary clinical question of interest is: What is the effect of MIJ821 (versus placebo) on change in Montgomery Asberg Depression Rating scale (MADRS) total score 24 hours after single s.c. injection compared to baseline assessment in participants with TRD who have already failed to adequately respond to at least two conventional antidepressants.
Secondary Objectives	To assess safety and tolerability of MIJ821 after single s.c. injection To assess MIJ821 pharmacokinetics (PK) in plasma after single s.c. injection To assess the duration of antidepressant effect of MIJ821 To characterize the dose-response and exposure-response relationship of MIJ821
Study design	This is a non-confirmatory, randomized, double-blind, placebo controlled, parallel-group trial. The study will enroll approximately 56 participants presenting with TRD. The study consists of a screening period (D-28 to D1), a treatment period (D1) and a 4-week follow-up period with an end of study (EOS) visit on Day 29. The maximum duration of the study, including screening, is approximately 8 weeks.
Rationale	This study will support the dose selection and dose regimen for future Phase 3 clinical trials by evaluating efficacy and safety of 3 doses of MIJ821 (1mg, 4mg and 10mg) administered subcutaneously, on top of pharmacological antidepressant standard of care (SoC) treatment in participants with TRD. [redacted]
Study population	Male and female participants, 18 to 65 years (inclusive), diagnosed with TRD.
Key Inclusion criteria	● Signed informed consent must be obtained prior to participation in the study ● Male and female participants,18 to 65 years of age (inclusive) at screening ● Participant has a diagnosis of recurrent major depressive disorder (MDD) and a current major depressive episode of at least 8 weeks in duration as defined by Diagnostic and Statistical Manual of Mental Disorders, Firth Edition (DSM-5) criteria and confirmed by both SCID-5 and adequate clinical psychiatric evaluation at Screening ● Participant obtains a MADRS score ≥ 24 at screening and before randomization on Day 1 ● Failure to respond to 2 or more prior antidepressant treatments but not more than 5, where two failed treatments are of two different antidepressants, with adequate dose and duration (≥ 6 weeks duration, doses defined per agent), as identified by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ), based on patient's report and prior psychiatric history, assessed by the investigator, and further documented by medical records. Patients with historical treatment failure to esketamine, ketamine or arketamine are excluded
Key Exclusion criteria	● Any prior or current diagnosis of MDD with psychotic features, bipolar disorder, schizophrenia, or schizoaffective disorder as obtained from SCID-5 at Screening ● Current acute depressive episode lasting longer than two years continuously, or participants receiving electroconvulsive therapy (ECT), transcranial magnetic

	stimulation (TMS), vagus nerve stimulation (VNS) or deep brain stimulation (DBS) in the current episode or within last year prior to Screening (whichever is longer) • Participants with acute alcohol or substance use disorder or withdrawal symptoms requiring detoxification, or participants who went through detoxification treatment (inpatient or outpatient) within 1 month prior to Screening, as obtained from SCID-5 at Screening • Participants with current borderline personality disorder or antisocial personality disorder as assessed at Screening, based on DSM-5 criteria and investigator judgment. • Current clinical diagnosis of autism, dementia, or intellectual disability • Participants with a history of suicidal attempt or suicidal behavior within one year prior to Screening and participants presenting suicidal ideation with intent documented by Columbia Suicide Severity Rating Scale (C-SSRS) with Yes response to question 4 or 5 at screening or baseline • Use of other investigational drugs at the time of screening, or within 30 days or 5 half-lives of screening, whichever is longer; or longer if required by local regulations • Pregnancy (including a positive human chorionic gonadotropin [hCG] test) or lactation at screening or baseline • Active hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) or active COVID-19 infections as per medical history and/ or available medical records • Resting QT interval corrected by Fridericia's formula (QTcF) ≥450 milliseconds (msec) (male) or ≥460 msec (female) at screening or baseline
Study treatment	MIJ821, placebo and pharmacological Standard of Care (SoC)
Treatment of interest	Participants who meet the eligibility criteria at screening and baseline will be randomized to one of the following four treatment arms and will receive a single s.c. injection on Day 1: (1) MIJ821 10 mg; (2) MIJ821 4 mg; (3) MIJ821 1 mg; (4) placebo. The overall randomization ratio is 1:1:1:1
Efficacy assessments	MADRS, Structured Interview Guide for MADRS (SIGMA) version, before and after s.c. injection and at each on-site visit in the follow-up period
Pharmacokinetic assessments	MIJ821 PK in plasma
Key safety assessments	Adverse event monitoring, physical examinations, monitoring of laboratory markers in blood and urine, electrocardiograms (ECGs)
[redacted]	[redacted]
Data analysis	To assess the efficacy, change from baseline in the MADRS score at 24 hours after single s.c. injection will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a group factor, class of antidepressant and baseline MADRS as a covariates, the Multiple Comparison Procedure - Modeling (MCP-Mod) methodology will be used to test the null hypothesis of a flat dose-response for the primary efficacy endpoint at a one sided significance level of 5% against the alternative hypothesis of a non-constant dose-response curve. If dose-response signal is detected, the MCP-Mod methodology, will also be employed to investigate the dose-response relationship.
Key words	Treatment-Resistant Depression; Major Depressive Episode; Major Depressive Disorder

1 Introduction

1.1 Background

1.1.1 Treatment resistant depression

Depression is a serious and life-threatening condition with high rates of morbidity and a chronic disease course. It is a common illness worldwide, with more than 264 million people affected (WHO 2020). When long-lasting and with moderate or severe intensity, depression causes the affected person to suffer greatly, impairing the ability to work, self-care, and maintain relationships.

Despite a broad availability of antidepressant medication, about a third of patients suffering from MDD fail to respond fully to antidepressant treatment of adequate duration and dose, and the majority fail to maintain long-term response to standard antidepressants (Rush et al 2006). This chronicity of symptoms predisposes patients to treatment resistance.

Treatment-resistant depression (TRD) is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate dosages for adequate durations.

Patients suffering from TRD are very likely to have suicidal ideation and experience a disproportionate burden of illness causing significant impairment and increased morbidity (Shelton et al 2010).

Therefore, there is a high unmet medical need for rapid-acting antidepressants that are either more effective or better tolerated, treatments that can effectively interrupt a depressive episode and are able to prevent future depressive episodes.

Ketamine, which is a N-methyl-D-aspartate (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 N-methyl-D-aspartate (NMDA) receptor inhibition as a rapid-onset antidepressant mechanism.

SPRAVATO® (esketamine), a non-competitive NMDA receptor antagonist, is approved for the treatment of TRD and is also approved for MDD with acute suicidal ideation or behavior by the Food and Drug Administration (FDA) and for moderate to severe episode of MDD as acute short-term treatment in conjunction with an oral antidepressant for the rapid reduction of symptoms which according to clinical judgement constitute a psychiatric emergency by the European Medicines Agency (EMA]). While both ketamine and SPRAVATO have demonstrated a certain level of efficacy and showed rapid mode of action, their safety profiles are not without adverse effects meaningful both for patients and clinicians.

Targeting a specific subset of NMDA receptors is one approach to potentially mitigate adverse effects of NMDA receptor inhibition while retaining the antidepressant efficacy. Preskorn (Preskorn et al 2008) demonstrated that infusion of traxoprodil, a negative allosteric modulator selective for the NR2B subtype of NMDA receptors, also known as CP-101,606, was efficacious in TRD patients with the magnitude and duration of response comparable to those

of ketamine with low potential to produce dissociative effects in patients. Ibrahim et al (Ibrahim et al 2012) reported that MK-0657 (Rislenemdaz, a selective NR2B antagonist) did not induce dissociative effects in TRD patients and was generally safe. Taken together, this suggest that achieving safe, yet rapid-onset antidepressant efficacy is feasible with a compound selectively inhibiting NR2B receptor.

1.1.2 MIJ821 Preclinical summary

MIJ821 is a highly potent, selective and reversible low molecular weight negative allosteric modulator (NAM) targeting the NR2B sub-unit of the N-methyl-D-aspartate receptors (NMDARs).

The primary pharmacological properties of MIJ821 were characterized *in vitro* and *in vivo* and established a pharmacological basis for the intended clinical use. Non-clinical drug disposition and exposure effect were assessed. *In vivo*, MIJ821 was shown to distribute into the rat brain.

The non-clinical safety profile of MIJ821 was evaluated in rats and dogs using the intravenous (i.v.) bolus route in studies of up to 6 weeks in duration. The choice of rats and dogs as preclinical species is justified by the relevance of these species in terms of pharmacology and metabolism. Key findings were as follows:

- While MIJ821 shows some in vitro off-target activity below 1 micromolar (µM), the risk of off-target pharmacology at therapeutically relevant exposures is considered low.
- In safety pharmacology, MIJ821-related findings included cardiovascular effects (human Ether-à-go-go-Related Gene (hERG) channel potassium current inhibition half maximal inhibitory concentration (IC50) = 1.1 µM; increased heart rate in dogs) and, in rats, lack of pinna response and increased respiration rate.
- In pivotal 6-week Good Laboratory Practice (GLP) studies, MIJ821 given i.v. twice a week was tolerated with no adverse effects and the top dose of 10 mg/kg was defined as the no observed adverse effect level (NOAEL) in rats and dogs. The main targets identified included the Central Nervous System (CNS) (clinical signs assumed to represent exaggerated pharmacological effects) and the cardiovascular system (as seen in safety pharmacology). There were no MIJ821-related local findings at the i.v. infusion or subcutaneous (s.c.) injection sites.
- MIJ821 did not induce neuronal vacuolation or necrosis.
- MIJ821 is not genotoxic or phototoxic.
- Embryo-fetal development (EFD) studies in rats and rabbits (daily i.v. administration during gestation) showed that MIJ821 is not teratogenic. In rats, MIJ821 was well tolerated. In rabbits, doses ≥ 9 mg/kg/day were above the maximal tolerated dose (MTD) for maternal animals and caused embryo lethality.
- NOAELs were identified in all pivotal studies with safety margins adequate for the pursued indication.

Further details are provided in the Investigator's Brochure (IB).

1.1.3 MIJ821 Clinical summary

The MIJ821 clinical development program aims to evaluate MIJ821 as a short-term, fast-acting treatment for adult participants with MDD who have acute suicidal ideation and behavior (initial indication) and as a treatment of adult participants with TRD (follow-on indication).

MIJ821 has been studied in a Phase 1 First-In-Human study (FIH, CMIJ821X2101) in healthy volunteers (HV) and in a Phase 2a Proof-of-Concept (PoC CMIJ821X2201) clinical study in participants with TRD after i.v. administration. A Phase 1 study is also ongoing to investigate the safety, tolerability and pharmacokinetic (PK) of subcutaneous MIJ821 in HVs (CMIJ821A02101).

First-In-Human study (CMIJ821X2101)

In a FIH study, MIJ821 was intravenously administered at single ascending doses (SAD) of 0.016, 0.048, 0.16, 0.24, 0.32, and 0.48 mg/kg (Part 1) and at repeated doses of 0.32 mg/kg given one week apart (Part 2) to HVs. Dissociative AEs, amnesia and sedation were observed at doses higher than 0.16 mg/kg.

In term of pharmacokinetics, no obvious PK difference has been identified between the two dosing events in the repeated dose part of the study.

PoC study in TRD participants (CMIJ821X2201)

This PoC study evaluated the safety and efficacy responses to MIJ821 in participants suffering from TRD (defined as failing two or more prior antidepressants, one in the current episode) assessed by the MADRS, a validated and widely employed method in depression trials (see details in Section 8.3.1). Participants were randomized with a ratio of 3:3:3:3:6:4 to one of six treatment arms: i) MIJ821 0.16 mg/kg one infusion per week (weekly), ii) MIJ821 0.16 mg/kg one infusion every other week (biweekly), iii) MIJ821 0.32 mg/kg weekly, iv) MIJ821 0.32 mg/kg biweekly, v) placebo weekly, and vi) ketamine 0.5 mg/kg weekly.

A total of 72 participants were randomized: 41 on MIJ821 across the 4 MIJ821 arms, 11 on ketamine and 20 on placebo. Out of these 72 participants randomized, 70 received study drug and were included in both efficacy and safety analyses. Two participants were randomized but did not receive study drug: 1 patient in MIJ821 0.32 mg/kg biweekly arm for physician decision and 1 patient in ketamine arm for adverse event before treatment. Overall, 53 (75.7%) completed the treatment and 50 (71.4%) completed the follow-up period. The most common reason for treatment discontinuation was participant/guardian decision (15.7%).

The primary endpoint of the study was the change from baseline in the total MADRS score at 24 hours after the start of the infusion compared to placebo. Both the MIJ821 0.16 mg/kg and the 0.32 mg/kg doses (pooled across weekly and bi-weekly dosing regimens) were superior to placebo on the primary endpoint. The MADRS adjusted arithmetic mean difference vs. placebo was −8.25 points (p=0.0013) for the pooled 0.16 mg/kg group and −5.71 points (p=0.0196) for the pooled 0.32 mg/kg group.

The safety and tolerability profile of MIJ821 was generally favorable across all the dosing regimens. The overall incidence of AEs was similar across the MIJ821 dose groups (61.9% for pooled 0.16 mg/kg and 68.4% for pooled 0.32 mg/kg) and the ketamine group (60.0%), which

were all higher than in the placebo group (35.0%). The most commonly reported AEs were amnesia (overall incidence across treatment groups: 14.3%), dizziness (14.3%), somnolence (11.4%), feeling abnormal (8.6%), headache (8.6%), depersonalization/derealization disorder (7.1%), fatigue (7.1%), dry mouth (5.7%) and nausea (5.7%).

Phase 1 study in HVs with s.c. MIJ821 (CMIJ821A02101)

This is a SAD study with randomized, participant and investigator blinded, placebo controlled design to investigate the safety, tolerability and PK of s.c. administered MIJ821 in healthy participants. The study is ongoing and will include approximately 32 non-Japanese and 12 Japanese participants. Study participants (non-Japanese) have already been enrolled into three sequential cohorts and received a single s.c. dose of 1, 4 or 12 mg MIJ821 or placebo. Eight participants completed treatment in each cohort with a randomization ratio 3:1 for MIJ821 to placebo. Subsequently, 12 Japanese participants will be enrolled into a single cohort and receive a dose of s.c. MIJ821 or placebo. The exact dose of MIJ821 in the Japanese cohort will be determined based on the results of the cohorts with non-Japanese participants.

Preliminary blinded data with s.c. MIJ821 are available from the ongoing double blind, placebo controlled SAD study (CMIJ821A02101). In this study, dissociative AEs were reported in the 4 and 12 mg cohorts, where MIJ821 exposure was comparable to that reached by 0.048 and 0.16 mg/kg i.v. doses in the FIH study, respectively. All of these events were mild or moderate in severity and resolved without treatment.

1.2 Purpose

The main purpose of this non-confirmatory study is to evaluate the safety and efficacy of a single s.c. MIJ821 injection in addition to standard pharmacological antidepressant (SoC) treatment in participants suffering from TRD assessed by the MADRS (Montgomery and Asberg 1979), a validated and widely employed scale in depression trials, evaluated 24h after study drug administration.

Furthermore, it is expected that this study will provide information about the dose-response and exposure-response relationship of the antidepressant effect of MIJ821 after single s.c. injection, which will be used to guide dose selection for confirmatory studies.

2 Objectives, endpoints and estimands

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 (versus placebo) in treatment resistant depression after single s.c. injection	● MADRS total score at 24 hours after s.c. injection compared to baseline assessment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To assess safety and tolerability of MIJ821 after single s.c. injection	● Incidence and severity of treatment-emergent adverse events (TEAEs), including AEs of special interest; standard safety assessments such as vital signs, ECG, hematology, blood chemistry, urinalysis; Clinician-Administered Dissociative States Scale

Objective(s)	Endpoint(s)
	(CADSS) score, Modified Observer's Assessment of Alertness/Sedation (MOAA/S), C-SSRS, memory assessment using orientation questions, results of local tolerability assessments
● To assess MIJ821 PK in plasma after single s.c. injection	● PK properties of MIJ821 in plasma described by Area under the curve from time zero to time of last measurable concentration (AUClast), maximum plasma drug concentration (Cmax), time to reach maximum plasma concentration (Tmax) (parameters not limited).
● To assess the duration of antidepressant effect of MIJ821	● MADRS total score at Day 8, 15, 22 and 29 visits compared to baseline
● To characterize the dose-response and exposure-response relationship of MIJ821	● Dose-response relationship of MIJ821 with respect to change from baseline in MADRS total score at 24 hours after single s.c. injection ● Exposure-response relationship of MIJ821 with respect to change from baseline in MADRS total score at 24 hours (Day 2)
[redacted]	

2.1 Primary estimands

The primary clinical question of interest is: What is the effect of s.c. MIJ821 (versus placebo) given in addition to standard pharmacological antidepressant (SoC) treatment 24 hours after the injection of the study drug on change in depressive symptoms in participants with TRD, who have already failed to adequately respond to at least two conventional antidepressants.

Rationale

The justification for the primary estimand is that it will allow to estimate the rapid effect of the study drug in a population of depressed participants, who are considered treatment resistant, based on the definition above. A rapid response is clinically valuable as conventional antidepressants might need several weeks to achieve reduction of depressive symptoms.

The primary estimand is described by the following attributes:

1. Population: participants with treatment resistant depression, who have failed to show adequate treatment response to at least 2 antidepressants previously.
2. Primary variable: change from baseline to 24 hours post dose in the MADRS total score.
3. Treatment of interest: the randomized treatment (the investigational treatment MIJ821 or the placebo treatment) administered as a single s.c. injection on Day 1. The dose of the allowed concomitant medication (i.e., SoC) for depression must remain stable during the trial.
4. Handling of intercurrent events (IEs) prior to MADRS assessment at 24 hours (for more details see Section 12.4.3):
    - New intake or change in concomitant medications/therapies which have a potential confounding effect: hypothetical strategy
    - Intake of prohibited medications: hypothetical strategy
    - Intake of rescue medications: hypothetical strategy
    - IEs related to pandemic: hypothetical strategy
    - IEs leading to study discontinuation due to adverse (AEs), lack of efficacy or other reasons: treatment policy

Participants who took prohibited medications, rescue medications, or took new or change concomitant therapy which have potential confounding effect, will continue in the study and be assessed as scheduled.

Further details about the concomitant therapy, prohibited and rescue medications are provided in Section 6.2.

The summary measure: difference in variable means between study drug and placebo.

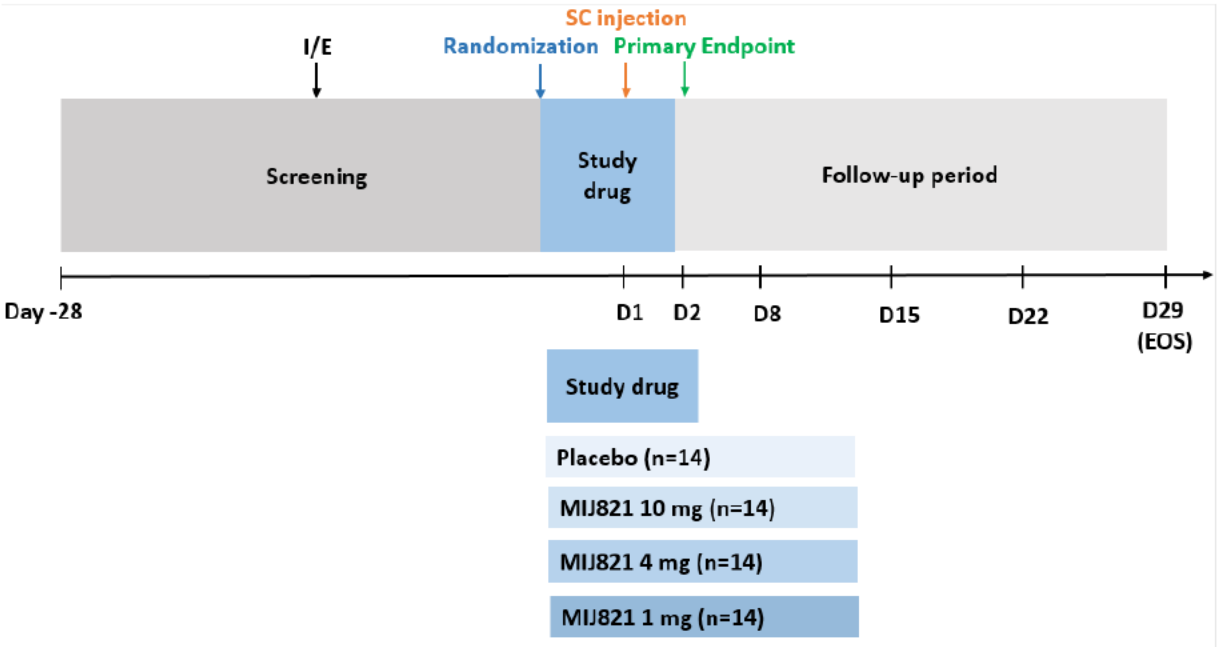
The Multiple Comparisons Procedures - Modeling (MCP-Mod) approach will be used to assess the primary objective (for more details on this approach see Section 12.4.2).

2.2 Secondary estimands

Not applicable

3 Study design

Figure 3-1 Study Design



This is a non-confirmatory, randomized, double-blind, placebo-controlled, parallel-group trial in participants with TRD to evaluate the efficacy, safety, tolerability and pharmacokinetics of single subcutaneous MIJ821 administration in addition to pharmacological antidepressant SoC treatment. Approximately 56 participants will be randomized in a total of 20-25 centers worldwide.

Participants will be randomly allocated to one of the following four treatment arms in a 1:1:1:1 ratio:

- Single administration of MIJ821 s.c. 10 mg
- Single administration of MIJ821 s.c. 4 mg
- Single administration of MIJ821 s.c. 1 mg
- Single administration of Placebo s.c.

The screening period starts when the participant signs the informed consent form and can last up to 28 days. The eligibility of participants is determined based on the assessments performed during the screening period and also on Day 1, prior to randomization. With the exception of lab results, all other baseline evaluations including the primary efficacy scale (MADRS) must be performed on Day 1, prior to randomization, and reviewed against the eligibility criteria before dosing. On Day 1, eligible participants will then be randomized to one of the above treatment arms.

Treatment is administered as a single s.c. injection on Day 1, followed by a safety observation at the clinical site for a minimum of 4 hours after administration. Study participants will be continuously observed by site personnel during the first 30 minutes after administration for emergence of adverse events, particularly CNS or cardiovascular AEs. Safety assessments will

include physical examinations (PEs), ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), administration of the CADSS, MOAA/S, C-SSRS, and memory assessment using orientation questions. Local tolerability will be evaluated by visual inspection of the injection area. Injection site abnormalities reaching the threshold of mild changes will also be assessed quantitatively (refer to Section 8.5.4).

Participants will be allowed to leave the clinical site at the earliest 4 hours after dosing, if all of the following criteria are fulfilled:

- The participant does neither report nor present with any CNS adverse events (dissociation, amnesia, sedation)
- There is no increase in suicidal intensity or new occurrence of suicidal ideation as assessed by C-SSRS
- No clinically relevant QTcF prolongation (QTcF≥500 msec or increase in QTcF from baseline≥60 msec)
- No clinically relevant abnormalities in blood pressure (BP) (90≤Sysotlic BP (SBP) ≥180 mmHg or 50≤Diastolic BP (DBP) ≥105 mmHg or increase or decrease in SBP of at least 20 mmHg or increase or decrease in DBP of at least 15 mmHg from baseline) or any increase in BP that is accompanied by symptoms, such as headache, dizziness, nausea, visual disturbances or other neurological symptoms
- The investigator does not identify any other AEs that require continued monitoring

If the participant cannot be released from the clinical site 4 hours after dosing, extended safety monitoring will be performed as described below.

The post-dose follow-up period will continue for 4 weeks (28 days) after treatment. On-site visits to assess efficacy and safety are scheduled on Day 2 (24 hours post-dose) and subsequently every week (i.e., on Days 8, 15, 22 and 29) during the follow-up period. The assessment to address the primary objective will be performed at Day 2 (24 hours post-dose). Phone calls will be conducted 3 days after each on-site visit with the exception of End-of-study (EOS) visit. The EOS visit will be completed on site on Day 29. The total duration of the study is approximately 8 weeks (56 days), including screening.

Extended safety monitoring in case of AEs on Day 1 (4 hours after dosing)

If extended monitoring is required beyond the minimum 4 hours of monitoring on Day 1, the following will be assessed:

- Monitoring of CNS adverse events (dissociation, amnesia, sedation):
  - If there are any dissociative AEs, amnesia or somnolence/sedation present, the participant should be monitored at the clinical site until these AEs are fully resolved. If the dissociative AEs or cognitive symptoms do not resolve within 6 hours after onset, the participant will be required to stay at the clinical site for overnight monitoring and can be discharged after the assessments are completed on Day 2 and the AEs have resolved. The onset and resolution time of dissociative and cognitive AEs should be captured as accurately as possible. The following assessments are recommended to follow CNS AEs, whenever possible (e.g., participant is awake):

  - If dissociative AEs are present, it is recommended to administer the CADSS every hour until the total score returns to baseline or normal level (i.e., total score not higher than 4)
  - If memory gaps/amnesia is present, it should be assessed with orientation questions at least once per hour until the amnesia is resolved
  - Sedation/somnolence should be assessed by questioning or the administration of the MOAA/S every hour until the AE is resolved
- Monitoring of suicidal ideation or behavior:
  - If moderate to severe suicidal ideation or any suicidal behavior is present, either based on rating scales or investigator judgment, the investigator must hospitalize the participant at least overnight
  - If suicidal ideation is mild, either based on rating scales or investigator judgment, the investigator's judgment can be used to allow the participant to leave the clinical setting, but in that case arrangements should be made such that family members or friends are present with the participant for at least 24 hours. If such arrangements cannot be made, it is recommended that the participant is hospitalized at least overnight
- Monitoring of QTcF prolongation:
  - If the initial QTcF prolongation is confirmed by repeated ECG at least 10 minutes later, close observation of the participant should be initiated at the investigator's discretion
  - ECG should be performed every 30 minutes until QTcF is below 500 msec and the increase from baseline is less than 60 msec
  - Serum electrolyte levels should be determined and corrected, if needed (in particular hypokalemia, hypomagnesemia)
  - Consultation with a cardiologist can be performed at the investigator's discretion
- Monitoring of increased blood pressure:
  - Increase in blood pressure should be monitored but initial treatment is not recommended unless clinically indicated. Blood pressure increase associated with MIJ821 treatment is usually transient and the blood pressure typically returns to pre-dose values within 3-4 hours
  - At 1.5 hours post-dose, if SBP is ≥160 mmHg and/or the DBP ≥100 mmHg, assessments should continue every 30 minutes until:
    1. The blood pressure is <160 mmHg SBP and <100 mmHG DBP, or
    2. As per investigator's clinical judgment, the participant is clinically stable, or
    3. The participant is referred for appropriate medical care, if clinically indicated
    4. If the blood pressure remains ≥ 160 mmHg SBP and/or / ≥100 mmHg DBP after 4 hours post-dose, the participant should be referred for immediate medical treatment

4 Rationale

4.1 Rationale for study design

4.1.1 Rationale for overall study design

The main purpose of the study is to investigate the efficacy of MIJ821 after single s.c. injection, on top of pharmacological antidepressant SoC treatment, in participants with TRD. The design of this study has been selected to adequately assess the primary objective and follows the treatment guidelines of the American Psychiatric Association (APA) treatment for depression (Alan J. et al 2010).

The randomized, placebo controlled design is intended to limit the effect of expectation bias and measurement bias. A parallel design has been selected to ensure unbiased comparison between the treatment arms. This design also avoids any potential carry over effect that might arise in a different design, such as cross-over.

Three MIJ821 arms with different doses are included in the study to allow estimation of the dose-response and exposure-response relationship of the antidepressive effect of MIJ821. This data will be used, [redacted] to select doses for the future pivotal studies in TRD.

[redacted] This information will be used to select the dosing interval for pivotal Phase 3 studies.

The study includes a frequent visit schedule, with weekly on-site visits and phone calls in between, for safety and efficacy assessments.

In a previously completed PoC study (MIJ821X2201) in TRD participants, the efficacy of MIJ821 has been evaluated after i.v. administration. [redacted]

4.1.2 Rationale for choice and timing of efficacy assessments

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. The 24-hour post-dose time point was chosen for the primary analysis to collect information about the expected rapid effect of MIJ821. Achieving a rapid antidepressant effect is clinically meaningful, as participants with major depression are at risk of suicide or self-harm, while conventional antidepressant drugs might take several weeks to reach efficacy. [redacted]

4.1.3 Rationale for safety assessments

The safety assessments and their frequency were selected based on the completed FIH (CMIJ821X2101) and PoC (CMIJ821X2201) studies and the ongoing SAD (CMIJ821A02101) study with s.c. MIJ821 in healthy volunteers.

The most common AEs associated with MIJ821 include dissociative events/amnesia and sedation. These will be monitored using AE collection, the CADSS and the MOAA/S, which were used to identify relevant events in previous studies with MIJ821.

Other potential risks associated with MIJ821 are QTc prolongation and increase in blood pressure. These events are associated with Cmax of MIJ821 and tend to decline during the first 4 hours after administration. Therefore frequent ECG and BP measurements will be performed during the first 4 hours after injection to identify any potential effect on QTc and BP.

Additional safety assessments include standard lab tests (hematology, blood chemistry, and urinalysis), physical examination and monitoring of AEs and SAEs. As participants with MDD or TRD are at risk of suicide, the C-SSRS will be used at every visit to monitor suicidal thoughts and behavior.

4.1.4 Selection of patient population

The study intends to investigate MIJ821 in participants with TRD, where a potentially rapid acting antidepressant drug can be beneficial. Treatment resistance will be defined based on retrospective assessment of previous treatment regimens and their outcome by the investigator and supported by medical records. [redacted]

Other eligibility criteria (Section 5) are defined to ensure a homogenous study population and minimize the risk associated with study participation.

4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Dose rationale

The three dose levels for the current study were selected based on exposure and receptor occupancy (RO) simulations after s.c. and i.v. administration of MIJ821 and preliminary safety, tolerability information from the ongoing SAD study with s.c. MIJ821 (CMIJ821A02101). In the first instance, the highest dose of s.c. MIJ821 was selected with the expectation to provide full efficacy of the compound. Thereafter, the mid and low doses were selected to ensure that a broad dose and exposure range are tested in the study.

Selection of highest dose

[redacted]

The highest dose of s.c. MIJ821 was selected to match the plasma exposure (i.e. Cmax) and RO (i.e. maximum RO) to those after i.v. administration of 0.16 mg/kg MIJ821. The latter dose was efficacious in the PoC study with i.v. MIJ821 (CMIJ821X2201) and is the highest dose in the ongoing Phase 2b dose range study in MDD patients with i.v. MIJ821 (CMIJ821A12201). For 10 mg s.c. MIJ821, a mean Cmax of 73 ng/mL (range: 36 – 105 ng/mL) was simulated, which is only 18% lower than the simulated mean Cmax after i.v. administration of 0.16 mg/kg MIJ821 (89 ng/mL, range: 64 – 125 ng/mL). Similar mean maximum RO values were simulated for both routes of administration at s.c. 10 mg (95%) and at 0.16 mg/kg (96%).

In the ongoing SAD study with s.c. MIJ821 (CMIJ821A02101), preliminary results identified dissociation as the most common AE (see Section 1.1.3 for details). The incidence of dissociation in the SAD study was higher with increasing doses of s.c. MIJ821. At the highest dose tested in the SAD study (12 mg MIJ821 s.c.), mild to moderate dissociation occurred in approximately 66% of the participants. The safety, tolerability and PK of s.c. MIJ821 might be slightly different in TRD patients than in HVs. Therefore, the highest dose of s.c. MIJ821 selected for the current study is 10 mg, which is slightly lower than the highest dose of s.c. MIJ821 (12 mg) tested in the SAD study (MIJ821A02101).

In summary, 10 mg MIJ821 administered via s.c. route is expected to achieve comparable RO profile to 0.16 mg/kg MIJ821 administered i.v., which is known to be efficacious in TRD. The 10 mg dose of s.c. MIJ821 is also expected to provide an acceptable safety and tolerability profile in TRD patients.

Selection of mid and low dose

The mid and low doses of s.c. MIJ821 in the current study were selected to minimize the overlap between MIJ821 exposure obtained in the different treatment groups and to cover a broad exposure range. The mean simulated Cmax (18 ng/mL) of s.c. MIJ821 at the mid dose of 4 mg dose is approximately 4.1-fold lower than the mean simulated Cmax at the highest dose of 10 mg (73 ng/mL). The mean simulated Cmax of s.c. MIJ821 (4 ng/mL) at the low dose of 1 mg dose is approximately 4.5-fold lower than the mean simulated Cmax at the mid dose of 4 mg (18 ng/mL). The estimated mean maximum ROs of s.c. MIJ821 are 95%, 84% and 54% at the 10 mg, 4 mg and 1 mg doses, respectively. These doses are therefore expected to reach a broad range of maximum RO values. Furthermore, there is a 10-fold difference between the lowest (1 mg) and highest (10 mg) dose of s.c. MIJ821 used in the current study, which is recommended by European Medicines Agency for dose range finding studies EMA 2015.

In summary, the selected doses of s.c. MIJ821 (1 mg, 4 mg, and 10 mg), cover a 10-fold dose range, yield a broad simulated exposure range with minimal risk of exposure overlap between dose levels and are also expected to provide a broad range of maximum RO values.

4.2.2 Rationale of treatment duration

The main purpose of the study is to assess the efficacy of MIJ821 to rapidly reduce depressive symptoms. As explained in Section 1, a rapid response is meaningful in TRD, a population that failed to respond to conventional antidepressants used for adequate duration of time and at adequate dose. Depression often leads to suicidal thoughts or behavior, putting patients at risk. However, conventional antidepressant treatment might take a few weeks to achieve treatment

benefit. There is thus a need for rapid acting, safe antidepressant treatments. To assess, whether MIJ821 can rapidly improve symptoms of TRD after s.c. administration, a single dose treatment is sufficient.

[redacted]

In the completed PoC study (CMIJ821X2201), MIJ821 was superior to placebo in reducing depressive symptoms measured by the MADRS total score at 24 hours after the first administration. MIJ821 also was significantly better than placebo after repeated dosing for 6 weeks when administered at 0.16 mg/kg dose bi-weekly or at 0.32 mg/kg dose weekly. The other two dose groups (0.16 mg/kg weekly and 0.32 mg/kg bi-weekly) also showed numerical improvement on MADRS score, but the difference from placebo was not significant, which might be due to the smaller sample size at week 6 compared to 24 hour post dose timepoint. Nevertheless, the PoC results demonstrate that the early response (24 hour post first dose) to MIJ821 and the results of repeated administration (6 week results) were similar, suggesting that the early response might be indicative of longer term results. In the PoC study (CMIJ821X2201), the maximum improvement of the MADRS score in the active treatment groups was already observed after the first drug administration (see Section 1.1.3). There was no further accumulation of the effect after later drug administrations. This suggests that a single drug administration is sufficient to estimate the maximum drug effect. It is therefore expected that results of the current study would predict results of longer treatment with repeated administration of MIJ821.

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

The use of a double-blind placebo arm against the MIJ821 arms is to provide a comparison group for an unbiased collection of efficacy, safety, and tolerability data. Based on the high degree of placebo response in depression trials, placebo is necessary to assess the efficacy of an investigational drug (Kirsch 2019).

4.4 Purpose and timing of interim analyses

An interim analysis, for internal modelling purposes will be performed after approximately 28 participants have completed the study at Day 29 (or discontinued prior to Day 29). The purpose of this interim analysis will be outside of study goals. This interim analysis for internal modelling purposes will be conducted by unblinded pharmacometric members. The unblinded results of the interim analysis for internal modelling purposes will not be communicated to the blinded study team.

Further interim analysis might be performed at any time during the study to support decision making concerning the current clinical study, the sponsor's clinical development plan or in case of any new safety concerns.

4.5 Risks and benefits

The available safety information, combined with the potential of MIJ821 to effectively treat depressive symptoms in patients, suggests a favorable risk-benefit ratio.

Risks associated with MIJ821

The risks associated with MIJ821 are summarized in Table 4-1, together with relevant preclinical and clinical findings, monitoring and mitigation of risks in the current study. The compound related risks were identified in preclinical and clinical studies with MIJ821 and from the literature with drugs with similar mechanism of action.

MIJ821 is an investigational drug that has been tested in a limited number of healthy volunteers (HVs) and patients with treatment resistant depression (see Section 1 and the Investigator Brochure for details). Risks for MIJ821 as a single agent were identified based on the available pre-clinical and clinical data from MIJ821 as well as data from drugs with similar mechanism of action (MoA), i.e. non-competitive NMDA receptor antagonists. There may be risks associated with MIJ821 that have not been identified yet.

In addition to the above-mentioned important risks, taking into account the class-effects with ketamine, and those anticipated due to subcutaneous infection, other potential risks associated with MIJ821 include the following events:

Table 4-1 Risks associated with MIJ821

Target organ/Risk; Relevant non-clinical and clinical findings with MIJ821	Monitoring and mitigation in the current study
CNS / Dissociative reactions, Amnesia ● CNS effects in rats: ● Lack of pinna response at 3 mg/kg in modified Irwin test ● 30 mg/kg/day in preliminary 2-week study: clinical signs, such as ataxia, abnormal gait, impaired righting reflex, decreased motor activity, muscle twitches, labored respiration, and/or rales and mortality ● At lower doses: no findings ● CNS effects in dogs: ● At all doses (1 to 10 mg/kg): transient clinical signs with dose-dependent severity (abnormal gait, decreased activity, impaired coordination, partially closed eyes and salivation) ● In the preliminary study: clonic-tonic convulsions in one dog on a non-dosing day following treatment at 3 mg/kg. No such finding in the pivotal study at same dose levels ● CNS-related clinical signs in rats and dogs are considered to be exaggerated pharmacological effects of MIJ821. ● FIH study relevant results ● Dissociative AEs were among the most common AEs in the study. They were dose dependent, but not observed at 0.16 mg/kg i.v. dose or lower. The range for time to onset from start of infusion was 0.78-3.43 hours and the time to resolution from onset was 1.15-5.35 hours after a single dose of MIJ821. ● Amnesia was also among the most common AEs in the study. It was observed at 0.32 and 0.48 mg/kg i.v. dose. The range for time to onset was 0.83-7.83 hours after start of infusion and the time to resolution from onset 0.02-23.85 hours after a single dose of MIJ821.	● Monitoring at the clinical site for minimum 4 hours on the day of MIJ821 administration and longer, if any dissociative or amnestic AEs are observed ● Routine AE collection and routine memory assessment questions ● Routine AE collection and regular administration of the CADSS ● Participants with current diagnosis and history of neurological or psychiatric disorders (including drug and alcohol abuse) other then TRD will be excluded

● J-ESS study relevant results

● No dissociative AEs or amnesia were reported in the study at any dose of i.v. MIJ821 (0.016-0.16 mg/kg).

● SAD study with s.c. MIJ821 (study ongoing, preliminary results from the first cohorts see Section 1.1.3 for details)

● Preliminary, blinded data with s.c. MIJ821 are available from the ongoing double blind, placebo controlled SAD study (MIJ821A02201). In this study, Dissociative AEs were reported in the 4 and 12 mg cohorts, where MIJ821 exposure was comparable to that reached by 0.048 and 0.16 mg/kg i.v. doses in the FIH study, respectively. All of these events were mild or moderate in severity and resolved without treatment.

● PoC study relevant results

● Dissociative AEs were among the most common AEs in the study and were observed at both doses used in the study (0.16 and 0.32 mg/kg, i.v.). The time to onset was quick (up to 0.7 hour after start of infusion), and the time to resolution ranged from 1.6 to 7.0 hours after onset.

● Amnesia was also among the most common AEs in the study, it was also observed at both 0.16 and 0.32 mg/kg i.v. doses with higher incidence at the higher dose. The time to onset was also quick (up to 0.7 hour after start of infusion), and the time to resolution ranged from 0.7 to 9.2 hours after onset.

CNS / Suicidality

● FIH and J-ESS study relevant results

● No relevant findings were identified based on AEs and the C-SSRS scale.

● PoC study relevant results

● Most subjects did not have suicidal behavior or suicidal ideation, indicated by the median score for both Sheehan-Suicidality Tracking Scale (S-STS) suicidal behavior subscale and S-STS suicidal ideation subscale, which were 0 in each treatment group at 24 hours, 48 hours and Week 6.

● There were 3 SAEs reported in 2 patients. One patient in the MIJ821 0.32 mg/kg biweekly treatment group had suicidal threat during the double-blind treatment period and suicide attempt during the follow-up period (approximately 6 weeks later). One subject in the placebo group reported suicide attempt. None of these events were considered study drug related. In another patient in the placebo group presented suicidal ideation, which was not an SAE, but was considered study drug related and lead to discontinuation of treatment.

● Monitoring at the clinical site for minimum 4 hours on the day of MIJ821 administration and longer, if the participant has severe suicidal ideation

● Routine AE collection

● C-SSRS scale will be administered repeatedly at every visit at the clinical site

● Participant with recent severe suicidal ideation or behavior are excluded from the study

Cardiovascular system / QT prolongation

● Non-clinical tox findings:

● hERG channel IC50 of 1.1 μM

● Late hNav1.5 current IC50 of 6.05 μM

● In dogs: transient increases in heart rate and related shortening of the PR and QT intervals, considered non-adverse (transient and of modest magnitude)

● FIH study relevant results

● There were no arrhythmic events of clinical significance, and no clinically relevant abnormalities were identified on the numerical ECG variables in the Holter and standard safety ECG.

● Concentration-response (CR) analysis revealed a positive correlation between the MIJ821 plasma concentration and the placebo-adjusted mean change from baseline in QTcF (ΔΔQTcF). The mean ΔΔQTcF

● Frequent ECG monitoring, particularly during the first 4 hours after study drug administration

● Routine AE collection

● Patients with history of cardiac disorders or QTcF ≥450 msec (male) or ≥460 msec (female) are excluded from the study

exceeded the threshold of 5 ms at the Cmax of 0.16 mg/kg (6.3 ms). The upper bound of the two-sided 90% CI remained below 10 ms at exposures below the Cmax of 0.16 mg/kg. ● J-ESS study relevant results ● CR analyses revealed a positive correlation between the MIJ821 plasma concentration and ΔΔQTcF. The mean ΔΔQTcF was 5.584 ms and the upper bound of the two-sided 90% CI was 11.732 ms at the geometric mean Cmax of 0.16 mg/kg dose. ● PoC study relevant results ● One subject (0.32 mg/kg MIJ821 biweekly) had new-onset atrial fibrillation recorded as an SAE, which was not considered study drug related.	
Cardiovascular system / Increased blood pressure ● FIH study relevant results ● CR analyses also revealed positive correlations between the MIJ821 plasma concentration and the placebo-adjusted mean change from baseline in systolic and diastolic blood pressure (ΔΔSBP and ΔΔDBP). ● The mean ΔΔSBP and mean ΔΔDBP at the Cmax of 0.16 mg/kg was 18.6 and 10.7 mmHg, respectively. ● J-ESS study relevant results ● CR analysis revealed a positive correlation between MIJ821 plasma concentration and placebo-adjusted change from mean baseline in the systolic and diastolic BP (SBP and DBP). ● At the geometric mean Cmax MIJ821 0.16 mg/kg, the mean ΔΔSBP and ΔΔDBP were 23.852 and 16.413 mmHg, respectively. ● PoC study relevant results ● Increased blood pressure was reported as AE in 3 subjects receiving MIJ821 (2 subjects in the MIJ821 0.16 mg/kg weekly treatment group, and 1 subject in the MIJ821 0.16 mg/kg every other week treatment group). All these elevations were detected within 2 hours after administration of study treatment. All these AEs were of mild or moderate severity and resolved on the same day or next day without intervention except one of the AEs in one subject (MIJ821 0.16 mg/kg every other week) which lasted more than 1 week (from Day 29 to Day 37).	● Frequent monitoring of vitals, particularly during the first 4 hours after study drug administration ● Routine AE collection ● Patients with Grade 2 or higher grade hypertension are excluded from the study

- Sedation

Sedation is a known class effect for NMDA inhibitors. Administration of MIJ821 was associated with development of sedation in early clinical studies. In early studies, sedation showed dose dependence, the time to onset for sedation was short, and most events occurred within 40 minutes of infusion.

Sedation in the current study will be monitored by AE collection and by the MOAA/S scale.

Given that MIJ821 may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, participants should be advised about these potential risks. If the participant is feeling drunk or dizzy or if he/she experiences visual disturbances, hallucinations, or euphoric mood, then he/she should not drive, use machines or perform any other tasks that require his/her attention and good coordination. In case of a safety concern, the participant should be hospitalized (or hospitalization should be

prolonged) as per investigator's judgement until resolution of these events or absence of a safety risk.

- Respiratory effects

MIJ821 demonstrated an increase in respiration rate of 23% at 3 mg/kg in the rat FOB/respiratory safety pharmacology study. However, ketamine might have a negative impact on respiratory function when administered rapidly, particularly at high doses. Ketamine at anesthetic dosages is considered relatively safe because protective airway reflexes are preserved. There are no reports of respiratory distress with ketamine i.v. at dosages of 0.3-0.5 mg/kg with 40 minute infusions that have been administered in depression participants. In the PoC study, no specific respiratory effect related signal was noted.

Respiratory effects will continued to be assessed in the study using adverse event data.

- Cystitis or other lower urinary tract adverse events.

Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with Spravato (esketamine) nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in Spravato treated participants than in placebo-treated participants. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which included treatment for up to a year.

Cystitis and other urinary symptoms will be monitored in the current study by AE collection and urinalysis.

- Injection site reactions and hypersensitivity

The risks associated with s.c. administration includes injection site reactions and hypersensitivity. Results of the SAD study in HVs with s.c. MIJ821 indicate that local tolerability of MIJ821 administered via the s.c. route was good. Mild pain, pruritus and bruising occurred in each dose group. All events were mild and self limiting.

In general, hypersensitivity can manifest with itching, flushing, headache, nausea/vomiting, hypotension, urticaria, bronchospasm, or angioedema. In the event of a hypersensitivity reaction, assess and treat for anaphylaxis, if indicated, and initiate supportive care as per local practice. Fluids, vasopressors, corticosteroids, antihistamines, bronchodilators, and oxygen should be at hand.

Potential MIJ821-related risks to the fetus and prevention of pregnancies:

MIJ821 is not genotoxic. Pivotal EFD studies in rats and rabbits showed that MIJ821 is not teratogenic. While MIJ821 was well tolerated in rats in the absence of maternal or embryofetal toxicity, treatment of pregnant rabbits with MIJ821 was associated with embryo lethality at maternally toxic dose levels. The NOAEL for maternal and fetal effects was established at 3 mg/kg/day which is associated with an AUC-based safety margin of 5.9-fold when compared with 0.16 mg/kg human dose.

Taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study.

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 participant will not reliably comply, they should not be entered or continue in the study.

COVID-19 related risks

If the Coronavirus Disease (COVID-19) pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by Novartis. Phone calls, virtual contacts (e.g., teleconsult) or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again. The collection of samples may also be modified by the Sponsor and will be communicated to the Investigator.

Please refer to the Investigator's brochure on additional details on the risks and mitigation measures.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 8 weeks, from each participant as part of the study. The approximate volumes are mentioned in the informed consent form (ICF). Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1).

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

See the Section 8.5.3.1. on the potential use of residual samples.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

Approximately 56 participants with TRD will be randomized to receive either MIJ821 1 mg, MIJ821 4 mg, or MIJ821 10mg or placebo, in addition to standard pharmacological antidepressant SoC treatment, in a 1:1:1:1 ratio in a total of 20-25 centers worldwide.

TRD is defined based on retrospective assessment of antidepressant treatment failure as per treatment history, as specified in the Inclusion criteria below.

The investigator must ensure that all participants being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible participants.

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

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

5.1 Inclusion criteria

Participants 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 participants, 18 to 65 years of age (inclusive) at screening.
3. Participant has a diagnosis of recurrent MDD and a current major depressive episode of at least 8 weeks in duration as defined by DSM-5 criteria and confirmed by both the SCID-5 and an adequate clinical psychiatric evaluation at screening.
4. MADRS ≥ 24 at screening and before randomization on Day 1.
5. Failure to respond to 2 or more antidepressant treatments but no more than 5, where the two failed treatments are two different antidepressants and at least one of which was used in the current depressive episode, with adequate dose and duration (≥ 6 weeks duration, doses defined per agent), as identified by the MGH-Antidepressant Treatment Response Questionnaire, based on the patient's report and prior psychiatric history, assessed by the investigator, and further documented by medical records. Patients with historical treatment failure to esketamine, ketamine or arketamine are excluded.
6. Participant must agree to receive pharmacological standard of care treatment to treat their MDD (as determined by the treating physician(s) based on clinical judgement and protocol recommendations) during the trial duration.
7. If the participant is taking any other type of psychotropic drugs, the dose of these drugs needs to be stable, where a stable dose of psychotropic drugs is defined as no changes in dose or type of e.g. antipsychotics or mood stabilizers for at least 6 weeks prior to baseline (if applicable).
8. The antidepressant should be at a stable dose for at least 4 weeks before baseline. No new antidepressant initiated 6 weeks or less before baseline. No psychotherapy initiated 4 weeks or less before baseline.
9. Able to communicate well, and to understand and comply with study requirements.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study:

1. Current acute depressive episode lasting longer than two years continuously, or participants receiving electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) or deep brain stimulation (DBS) in the current episode or within last year prior to screening (whichever is longer).
2. Any prior or current diagnosis of MDD with psychotic features, bipolar disorder, schizophrenia, or schizoaffective disorder as obtained from SCID-5 at screening.
3. Participants with acute alcohol or substance use disorder or withdrawal symptoms requiring detoxification, or participants who went through detoxification treatment

(inpatient or outpatient) within 1 month before Screening, as obtained from SCID-5 at screening.

4. Participants with current borderline personality disorder or antisocial personality disorder assessed at Screening, based on DSM-5 criteria and investigator judgment.
5. Current clinical diagnosis of autism, dementia, or intellectual disability.
6. Participants with a history of suicidal attempt or suicidal behaviour within last year prior to screening and participants presenting suicidal ideation with intent documented by C-SSRS by Yes response to Q4 or Q5 at screening or baseline.
7. Participants with evidence of significant renal insufficiency, indicated by an estimated glomerular filtration rate (eGFR) of <40 mL/min/1.73 m2 at screening.
8. Use of other investigational drugs at the time of screening, or within 30 days or 5 half-lives of screening, whichever is longer.
9. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar mechanism of action (i.e. drugs that affect the NMDA receptor).
10. Active hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) or active COVID-19 infection as per medical history and/or available medical records.
11. History of seizures. Note: childhood febrile seizures are not exclusionary.
12. Cardiac or cardiac repolarization abnormality, including any of the following:
    - History of myocardial infarction, angina pectoris, or coronary artery bypass graft within 6 months prior to starting study treatment
    - History of clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II and third degree AV block) within 6 months prior to starting study treatment
13. Resting QTcF ≥450 msec (male) or ≥460 msec (female) at screening or baseline.
14. Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia or any of the following:
    - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
    - Concomitant medication(s) with a “Known Risk of TdP” that cannot be discontinued or replaced by safe alternative medication
15. Participant has mean systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg at Screening or pre first dose on Day 1; or past history of hypertensive crisis.
16. History of hemorrhagic stroke or known cerebrovascular disorders (e.g. aneurysm or arteriovenous malformation) or known aneurysmal vascular disease in other location (e.g. aorta).
17. Pregnancy (including a positive human chorionic gonadotropin [hCG] test) or lactation at screening or baseline.
18. 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 investigational drug. 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 participants on the study the vasectomized male partner should be the sole partner for that participant.
- Use of intrauterine device (IUD) or intrauterine system (IUS). In case of use of an IUD or IUS, the device or system should have been placed and well tolerated by the patient for a minimum of 3 months before taking the study treatment.

Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception other forms of hormonal contraception are not allowed for the purpose of contraception.

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 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).

19. 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.
20. Participants taking medications prohibited by the protocol (see Section 6.2.2)
21. Any other condition (e.g. known liver disease/liver dysfunction, active malignancy etc.) which in the opinion of the investigator would put the safety of the participant at risk, affect compliance or make the patient an unsuitable candidate for the study.

    General Note: In the case where a safety laboratory assessment at screening and/or baseline 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 participant is excluded from the study.

6 Treatment

6.1 Study treatment

Study treatment consists of MIJ821 or placebo. MIJ821 20 mg will be supplied centrally as lyophilized powder in vials (pharmaceutical form).

MIJ821 20 mg will be reconstituted with water for injection to obtain the solution for injection for all MIJ821 doses. Placebo will consist of 0.9% sodium chloride infusion bags supplied by the site.

The s.c. injection of study treatment (Day 1) must be administered while the participant is at site.

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

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
MIJ821 20 mg Lyophilisate in vial	Powder for solution for injection	Injection use (after reconstitution)	Open label supply, vials (one vial per kit)	Sponsor (global)
Placebo	0.9% sodium chloride solution	Injection use	Open label; infusion bag/bottle	Locally by site

The investigational treatment for this study is MIJ821. Due to the difference in preparation between MIJ821 and placebo, unblinded qualified site personnel, independent from the investigational staff, are required to maintain the blind. Please refer to Section 6.5 for additional details.

6.1.2 Additional study treatments

No other treatment beyond investigational drug, control drug (placebo), and pharmacological antidepressant SoC are included in this trial.

Pharmacological antidepressant SoC treatment in the study will consist in antidepressants or combinations of antidepressant with other drugs used for depression augmentation. It is recommended that antidepressants used as background therapy during the study are FDA approved for MDD indication (see protocol Appendix 6 Section 16.6: Antidepressants recommended to be used as background therapy during the study).

6.1.3 Treatment arms/group

Participants will be randomly allocated to one of the following four treatment arms in a 1:1:1:1 ratio, on Day 1:

- Single administration of MIJ821 10 mg, one s.c. injection
- Single administration of MIJ821 4 mg, one s.c. injection

- Single administration of MIJ821 1 mg, one s.c. injection
- Single administration of placebo, one s.c. injection

6.1.4 Treatment duration

Participants will receive a single s.c. injection on Day 1.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions, SARS-CoV-2 vaccine) administered after the participant was enrolled into the study must be recorded in the concomitant medications/significant non-drug therapies CRF.

The investigator should instruct the participant to notify the study site about any new medications he/she takes after the participant is enrolled in the study. All medications, procedures and significant non-drug therapies administered after the participant is enrolled into the study must be recorded. The start and stop date and time of each medication use should be recorded as precisely as possible.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication.

All allowed concomitant baseline psychotropic medications used for treatment of depression must be documented as Standard of Care (SoC) and remain unchanged throughout the study. Any change in SoC after randomization (dose changing or starting new drugs) should be documented in medical records and reported in the eCRF.

Certain benzodiazepines, specifically lorazepam or alprazolam (as authorized by country), will be allowed for episodic or chronic use. **These should not be taken within 12 hours before and within 4 hours after dosing unless it is used as rescue medication not to exceed 2 mg in a 24-hour period**. Such lorazepam or alprazolam use will be documented as concomitant medication(s) and administration time should be documented in medical records and reported in the eCRF.

Any vaccinations should not be administered within 2 days prior to randomization.

For participants taking strong CYP2D6 inhibitors (e.g., berberine, bupropion, dacomitinib, fluoxetine, paroxetine, quinidine), the immediate time period after s.c. administration should be monitored with extra caution. All safety observations should be carefully observed for increased or unexpected frequency and severity.

Based on nonclinical information, MIJ821 is predicted to be eliminated predominately by oxidative metabolism via CYP2D6 (64% of elimination). Inhibition of the elimination pathways may lead to an increase of MIJ821 exposure. The following investigations have been executed to assess the potential drug-drug interaction on the major elimination pathway via CYP2D6:

- The impact of strong CYP2D6 inhibitors (e.g., fluoxetine, paroxetine and bupropion) on the exposure of i.v. infused MIJ821 has been investigated in drug-drug interaction (DDI) simulations by means of the SimCYP® software. The simulated Cmax values were in

maximum 1.3-fold higher in the presence of fluoxetine or paroxetine and the AUC values in maximum 2-fold for all CYP2D6 genotypes (poor, extensive, or ultra-metabolizers). The resulting mean exposure values in the presence of strong CYP2D6 inhibitors are within the exposure range investigated in the FIH study after i.v. infusion (CMIJ821X2101, doses: 0.016, 0.048, 0.16, 0.24, 0.32 and 0.48 mg/kg). For the strong CYP2D6 inhibitor bupropion, no drug-drug interaction was estimated. Comparable impact of the MIJ821 exposure is expected after s.c. administration in the presence of strong CYP2D6 inhibitors since the i.v. and s.c. routes of administration are comparable in terms of circumventing the liver first-pass. Following s.c. administration of the highest dose (12 mg) in the s.c. SAD study with HVs (CMIJ821A02101), the exploratory mean AUClast and Cmax values are 257 h*ng/mL and 77.4 ng/mL, respectively, being comparable to the exposure values after i.v. infusion of 0.16 mg/kg MIJ821 in the FIH study (CMIJ821X2101). As discussed above, the mean exposure values after s.c. administration of the highest dose in this study (10 mg) are within the exposure range investigated in the FIH study in the presence of strong CYP2D6 inhibitors.

- Furthermore, in the PoC study (CMIJ821X2201, doses: 0.16 and 0.32 mg/kg), approximately 70% of participants received at least one CYP2D6 inhibitor (weak to strong CYP2D6 inhibitor or combinations of them). The Cmax values at both doses and the AUC values at 0.16 mg/kg do not exceed the exposure range determined in the FiH study.

Based on overall clinical experience (CMIJ821X2101, CMIJ821X2201), the totality of the safety data suggest that MIJ821 is generally safe and well tolerated and observed adverse events were transient. The risk of an overdose or unexpected AEs due to an exposure increase by CYP2D6 inhibition is considered to be low for the proposed MIJ821 doses being less or equal to 10 mg. In conclusion, CYP2D6 inhibitors are allowed as co-medications. Nevertheless, caution has to be taken when strong CYP2D6 inhibitors are administered.

Based on nonclinical information, MIJ821 may affect the elimination of compounds eliminated predominantly via CYP3A4 and CYP2D6. The impact of MIJ821 on the exposure of midazolam (CYP3A4 substrate) and desipramine (CYP2D6 substrate) has been investigated in drug-drug interaction (DDI) simulations by means of SimCYP® software. No exposure increase of both probe substrates has been estimated at the highest tested MIJ821 dose of 0.48 mg/kg after i.v. infusion. Therefore, the risk of an overdose or unexpected adverse events of co-administered sensitive CYP3A4 and CYP2D6 substrates is considered to be not significant at s.c. doses of ≤ 10 mg MIJ821.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Refer to Section 6.2.1.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed at the time points listed. This list of medications is not exhaustive. Each medication should be evaluated for its potential additive effect(s) of sedation, dissociation, suicidality, cardiovascular and respiratory effects, as well as impact on memory and cognitive functions. Medications with a potential impact should be avoided for at least one half-life of the medication before each study visit and one half-life after each study drug administration.

Table 6-2 Prohibited Medications or Treatment

Medication	Prohibition period	Action taken to study treatment**	Reason
Ketamine, Esketamine, Arketamine	2 months before Screening and during the whole study duration	Do not administer study treatment	Safety and PD interaction -additive effects (NMDA receptor antagonists)
ECT, transcranial magnetic stimulation (TMS), Deep brain stimulation (DBS), and Vagus nerve stimulation (VNS)	From screening and during the whole trial duration	Do not administer study treatment	PD interaction
Amantadine	From screening and during the whole trial duration	Do not administer study treatment	Safety (CNS additive effects) and PD interaction (weak non-competitive NMDA receptor antagonist)
Monoamine oxidase inhibitors (MAOIs)	From screening (minimum 14 days before baseline) and during the whole trial duration	Do not administer study treatment	Safety (additive risk of hypertension effect and potential for precipitating hypertensive crisis) and PD interaction
Citalopram, Escitalopram	From Screening and during the whole trial duration	Do not administer study treatment	Safety (additive risk of QT prolongation, known risk of Torsades de Pointes)
Medications with a Known Risk of Torsades de Pointes according to Section 16.5 and https://crediblemeds.org/	7 days before and 7 days after the study drug injection.	Do not administer study treatment	Safety (additive risk of QT prolongation, risk of Torsades de Pointes)
Amitryptyline, Nortryptyline	Within 24 hours prior to study drug injection and up to at least 4 hours after study drug injection	Do not administer study treatment	Safety (additive risk of QT prolongation, risk of Torsades de Pointes)
Quetiapine	Within 12 hours prior to study drug injection and up to at least 4 hours after study drug injection	Do not administer study treatment	Safety (additive risk of QT prolongation, risk of Torsades de Pointes)
Oral and Systemic Hormonal Contraceptives for contraception purposes	From Baseline and up to 1 week after study drug injection	Do not administer study treatment	Not accepted as highly effective contraception until a dedicated clinical study shows no drug-sruf interaction between MIJ821 and hormonal contraceptives.
Systemic Corticosteroids	Chronic use is prohibited from Screening and until the end of study	Do not administer study treatment	Safety (additive cardiovascular and neuropsychiatric effects)
Cough decongestants	Within 12 hours prior to study drug injection and up to at least 4 hours after end of study drug injection	Do not administer study treatment	Safety (additive sedative effects) and confounding effect for safety assessments
Benztropine and diphenhydramine	Within 12 hours prior to study drug injection.	Do not administer study treatment	Safety (additive sedative effect) and confounding

Medication	Prohibition period	Action taken to study treatment**	Reason
	Continuous use is prohibited.		effect for safety assessments
Benzodiazepines	Within 12 hours prior to and 4 hours after study drug injection	Do not administer study treatment	Safety (adding sedative effect and confounding effect for safety assessments)
Trazodone	Within 24 hours prior to and 24 hours after study drug injection	Do not administer study treatment	Safety (additive Risk of QT prolongation)
Alcohol	Within 24 hours prior to and 24 hours after study drug injection*	Do not administer study treatment	Safety (additive sedative and CNS effects), confounding effect for safety and efficacy assessments
Cannabis, medical marijuana and psychostimulants (amphetamines, methylphenidate, modafanil, armodafinil etc.)	Within 24 hours prior to each study visit and 24 hours after study drug injection*	Do not administer study treatment	Safety (additive CNS effects), confounding effect for safety and efficacy assessments
Opioids	Within 24 hours prior to each study visit and 24 hours after study drug injection*	Do not administer study treatment	Safety (additive sedative and CNS effects), confounding effect for safety and efficacy assessments
* In case of a prohibited use or when a participant appears intoxicated at the visit (e.g., alcohol, etc.), visit reschedule should be considered as per the permitted visit window ** Participants who are in the post dose follow-up period should continue the follow-up even if they are taking prohibited medications.			

6.2.3 Rescue medication

Rescue medications will not be supplied by the sponsor.

The following rescue medications may be considered and the use of these should be documented in the medical records and in the eCRF:

For agitation and anxiety or aggressive behavior (per investigator's judgment or local clinical practice): as required, midazolam (maximum dose 2.5 mg orally or intramuscular), any short-acting benzodiazepine (e.g., lorazepam), or antipsychotics (e.g., quetiapin, olanzapine, promethazin, or dipiperon).

Prohibited medication (see Table 6-2) can be administered as rescue medication at any time if clinically warranted.

6.2.4 Restriction for study participants

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

6.2.4.1 Dietary restrictions and smoking

No dietary or smoking restrictions in this study.

Participants should not consume alcohol or cannabis 24 hours before each study visit. If the participant appears intoxicated at the visit (e.g., alcohol, marijuana, other agent), a visit reschedule should be considered.

6.2.4.2 Other restrictions

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

6.3 Preparation and dispensation

Each study site will be supplied with the investigational treatment (MIJ821) in packaging as described under investigational and control drugs section (Section 6.1.1).

For the study treatment (MIJ821 or placebo) preparation prior to administration, please refer to the Pharmacy Manual.

Qualified unblinded site personnel will identify the study treatment to dispense to the participant by contacting the Interactive Response Technology (IRT). The investigational treatment (MIJ821) is labeled and a unique medication number is printed on the label. Immediately before dispensing the investigational treatment kit, the qualified unblinded personnel will report the unique medication number in the source document.

Placebo will be sourced locally. The study site must capture in the drug accountability log the name of the placebo manufacturer, the batch number and expiry date. For details on preparation, refer to the Pharmacy Manual.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a qualified unblinded site personnel at the study site, handled and stored safely, properly, and kept in a secured location to which only the qualified unblinded site personnel have access. Upon receipt, all study treatments must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Investigational treatment labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The qualified unblinded site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by unblinded monitors during site or remote monitoring visits, and/or at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the qualified unblinded site personnel may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the qualified unblinded site personnel will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis unblinded monitor or to the Novartis address provided in the investigator folder at each site.

6.3.1.2 Handling of other treatment

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

6.3.2 Instruction for prescribing and taking study treatment

Study participants will receive one of the following study treatments as a single s.c. injection: MIJ821 (10 mg, 4 mg, 1 mg) or placebo.

The study treatment will be administered as a single s.c. injection in the abdominal area, above (i.e., cranial to) the line of the umbilicus, but not within 5 cm from the umbilicus. The injection must not be administered in an area with scars, inflammation, proliferative skin disease (including nevus), tattoo, burn or other abnormalities of the skin. The injection must be administered by trained staff with appropriate technique and by considering the participant's body shape (e.g., thickness of local subcutaneous tissue). For thin participants, using the skin-fold technique is recommended. The injection will be administered slowly (over 15-30 sec). Care must be taken not to administer the study treatment as intramuscular injection, as that might change the PK and consequently the safety and efficacy profile of MIJ821.

Please refer to the Pharmacy Manual for further details.

Study treatment (MIJ821 or placebo) will be assigned by the IRT and will be recorded in the IRT system.

Each study site will be supplied with investigational treatment (MIJ821) kits as described in Section 6.1.1 (Investigational and control drugs).

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No. Re-screening for patients will only be allowed once.

6.4.2 Treatment assignment, randomization

On Day 1, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The qualified site personnel will contact the IRT after confirmation from the investigator or his/her delegate that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm. If the participant is allocated to the placebo treatment arm, IRT will not return any kit allocation. If the patient is allocated to the active treatment arm, IRT will assign a unique medication number.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by class of current anti-depressant standard of care (Selective Norepinephrine Reuptake Inhibitors (SNRI), Selective Serotonin Reuptake Inhibitors (SSRI) or other anti-depressants or combination of anti-depressants).

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

The unblinded qualified site personnel MUST NOT communicate information about medication numbers to anyone involved in the study (i.e., site personnel including the investigator, participant, sponsor) with the exception of the unblinded monitor and the clinical staff managing the drug supply to site. If accidentally communicated, the Novartis unblinded monitor should be notified.

6.5 Treatment blinding

Participants, investigator staff, and persons performing the assessments will remain blind to the identity of the treatment from the time of randomization until database lock using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions: GCS and the PK analysts team; (2) the identity of the treatments will be concealed by the involvement of unblinded qualified site personnel for study treatments preparation and administration.

Open label supply of MIJ821 will be provided to the unblinded qualified site personnel who must remain independent from other site staff in order to maintain the blind. The study treatments will be prepared by an unblinded qualified site personnel, and administration will be performed by an unblinded administrator. Both must be independent and not be involved in any study assessments. Preparation and administration of study treatments can also be performed

by a single unblinded qualified site personnel, if authorized to complete both activities. Instructions for prescribing/dispensing and administration are outlined in the Pharmacy Manual.

To minimize the risk of introducing bias, different site personnel must perform efficacy and safety assessments as described in Section 8.3.1 .

The randomization codes associated with participants from whom PK samples are taken will be disclosed to the PK bioanalyst, who will keep PK results confidential. The randomization codes may also be disclosed to designated pharmacometric team members.

At the time of interim analysis planned for internal purpose (i.e., when approximately 50% of participants have completed study (or discontinued prior to Day 29), the designated Novartis pharmacometric team members will be unblinded. The results of this interim analysis will be restricted to the designated pharmacometric members.

The Data Monitoring Committee (DMC) will conduct ongoing unblinded safety reviews. There will be unblinded statisticians and programmers in charge of DMC reporting activities (for more details on DMC, see Section 10.3.1).

Unblinding a participant at site, for safety reasons (necessary for participant management), will occur via an emergency system in place at site.

6.6 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

Injections will be administered at site. This information must be captured in the source document, the appropriate CRF(s) and in the Drug Accountability log.

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

6.7.2 Recommended treatment of adverse events

AEs must be treated according to local guidelines relevant for the symptoms.

Medication used to treat AEs must be recorded on the appropriate CRF.

6.7.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the

investigational drug treatment for the specified participant 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 IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- participant number

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

A participant cannot continue the study after an emergency break.

7 Informed consent procedures

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

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 participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 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 treatment can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant 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 participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, the Information Sheet for the Female Partner of Male Study Participants which highlights the need for the use of highly effective methods of contraception
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment

[redacted]

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 participants 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 after IRB/IEC approval.

Participants will be asked to complete an optional Trial Feedback Questionnaire (TFQ) to provide feedback on their clinical trial experience.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all study assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should attend on-site study visits as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. This is especially important for the Day 2 visit at which primary efficacy assessments are performed. Missed or rescheduled visits should not lead to automatic discontinuation. In addition, the participant will be contacted by phone in between on-site visits (Follow-up call) to collect information about adverse events and concomitant medications. In case follow-up calls have to be shifted by +/- 3 days, follow-up calls can be replaced by on-site visits in accordance to the original visit schedule.

In case a visit is performed outside the schedule, subsequent visits shall be performed in accordance to the original visit schedule. In addition to the scheduled visits, participants may have unscheduled visits for safety monitoring purposes at the discretion of the Investigator. Data collected during unscheduled visits will be recorded in the unscheduled visit CRFs.

Participants who discontinue from the study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, the adverse events and concomitant medications not previously reported must be recorded on the CRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Every effort will be made to draw the PK samples at the protocol specified timepoints. Other assessments (e.g., ECG, vital signs, etc.) will be taken prior to the PK sample.

[redacted]

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by Novartis as the situation dictates. If permitted/approved by local or Regional Health Authorities and Ethics Committees as appropriate and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	Screening	Treatment											Follow-up							
Visit Name	**Screening**	**Treatment**											**Follow-up call**	**Follow-up visit**	**Follow-up call**	**Follow-up visit**	**Follow-up call**	**Follow-up visit**	**Follow-up call**	**End of Study visit**
Visit Numbers[1]	**1**	**20**										**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**
Days	**-28 to -1**	**1**										**2**	**4**	**8**	**11**	**15**	**18**	**22**	**25**	**29**
Time (post-dose)	**-**	**-1h**	**0h**	**0.17h**	**0.33h**	**0.5h**	**0.75h**	**1h**	**1.5h**	**2h**	**4h**	**24h**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Informed consent	X																			
[redacted]																				
Inclusion / Exclusion criteria	X	X																		
Medical history/current medical conditions	X																			
SCID-5	S[3]																			
MGH-ATRQ	S[3]																			
Alcohol Test and Drug Screen	S[3]	S[3]																		
Pregnancy and assessments of fertility[4]	X	X[5]																		X
Demography	X																			
Body Height	X																			
Body Weight	X	X																		X
Physical Examination	S[3]																			S[3]

Period	Screening	Treatment											Follow-up							
Visit Name	Screening	Treatment											Follow-up call	Follow-up visit	Follow-up call	Follow-up visit	Follow-up call	Follow-up visit	Follow-up call	End of Study visit
Visit Numbers[1]	1	20										40	50	60	70	80	90	100	110	120
Days	-28 to -1	1										2	4	8	11	15	18	22	25	29
Time (post-dose)	-	-1h	0h	0.17h	0.33h	0.5h	0.75h	1h	1.5h	2h	4h	24h	-	-	-	-	-	-	-	-
Body Temperature	X	X										X								X
Blood Pressure and Pulse Rate	X	X[6]				X			X		X	X		X		X		X		X
Respiratory rate[3]	S	S				S			S		S	S		S		S		S		S
Oxygen Saturation		S[3,7]																		
Electrocardiogram (ECG)	X	X[6]				X			X		X	X								X
CADSS		X				X			X		X	X		X		X		X		X
MOAA/S		X				X			X		X	X		X		X		X		X
Memory Assessment Questions[13]						S					S	S								
C-SSRS	X	X									X	X		X		X		X		X
Local tolerability assessment						S					S	S								
Hematology	X[11]	X										X								X
Clinical Chemistry	X[11]	X										X								X
Coagulation Panel	X[11]	X										X								X
Urinalysis	X[11]	X										X								X
PK blood collection [12]			X[8]	X	X	X	X	X	X	X	X	X[9]								

Period	Screening	Treatment											Follow-up							
Visit Name	Screening	Treatment											Follow-up call	Follow-up visit	Follow-up call	Follow-up visit	Follow-up call	Follow-up visit	Follow-up call	End of Study visit
Visit Numbers[1]	1	20										40	50	60	70	80	90	100	110	120
Days	-28 to -1	1										2	4	8	11	15	18	22	25	29
Time (post-dose)	-	-1h	0h	0.17h	0.33h	0.5h	0.75h	1h	1.5h	2h	4h	24h	-	-	-	-	-	-	-	-
[redacted]																				
Randomization		X																		
Dose administration			X																	
MADRS	X	X									X	X		X		X		X		X
[redacted]																				
[redacted]																				
Concomitant therapies	X	X										X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X		X		X			X	X	X	X	X	X	X	X	X	X	X
Study completion information																				X
Safety follow-up call													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] Optional for participant
[3] 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 randomized.
[4] Additional pregnancy testing may be performed at each visit to meet local requirements. Serum pregnancy test to be performed, unless specified otherwise.
[5] Urine pregnancy test. Dosing can proceed only if result is negative.
[6] Dosing can proceed if the results are deemed satisfactory by the Investigator.
[7] Every 15 minutes from pre-dose to 4 hours post-dose
[8] Pre-dose
[9] Approximately 24 hours after the injection
[redacted]
[11] All screening laboratory results must be obtained before randomization to ensure participants eligibility
[12] In case of unscheduled visits for safety monitoring purposes during the time period from 4 hours to 24 hours after injection, unscheduled PK samples may be collected if operationally feasible.
[13] The outcome of this assessment will only be captured in the eCRF if amnesia is considered as an AE

8.1 Screening

Screening

Investigators may re-screen a participant only once if the investigator is reasonably certain that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Reasons to re-screen may include but are not limited to the following:

- Laboratory value(s) out of range due to sampling error or that might be within range after medically-appropriate supplementation
- The participant has a medical condition that can be stabilized or resolved prior to the repeat screening attempt
- Additional time is required following the participant's last dose of an excluded medication (see Table 6-2)

A participant must provide a new informed consent prior to the initiation of any re-screening procedures (e.g. participant must be reconsented). A new subject number will be assigned.

8.1.1 Eligibility screening

8.1.1.1 Hepatitis screen, HIV screen

Not applicable.

8.1.1.2 Alcohol test, Drug screen, Urine cotinine

Participants will be tested for substances of abuse (e.g. alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates).

Positive results will not be exclusionary if the participant doesn’t meet DSM-5 criteria for substance use and inclusion would be the responsibility of the Investigator.

This will be recorded as source data only by the use of an "S" for the corresponding criteria in Table 8-1 (Assessment Schedule) of the protocol.

8.1.2 Information to be collected on screening failures

Participants who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and the Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during screening phase (see SAE Section 10.1.3 for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error will be considered an early terminator. The reason for early termination should be recorded on the appropriate CRF.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participant demographic, socio-economical and baseline disease characteristic data will be collected on all participants. Relevant medical history/current medical conditions present prior to signing the informed consent will be recorded. Investigators have the discretion to record abnormal test findings on the medical history eCRF, if in their judgment, the abnormality occurred prior to the informed consent signature.

Participant demographics: full date (if permitted) or year of birth, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, we need to assess the diversity of the study population as required by Health Authorities.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

8.3.1 Handling of Efficacy Assessments by Independent Site Raters

The primary efficacy endpoint of MIJ821 compared with placebo is assessed based on the MADRS scale, SIGMA version.

Administration of MIJ821 is associated with a number of transient adverse events, including sedation, dissociative symptoms, memory gaps/amnesia and cardiovascular events. To minimize the risk of introducing bias, trained and qualified site personnel will perform efficacy and safety assessments. Independent site raters who perform the MADRS, [redacted] will be different from those who evaluate vital signs, adverse events, ECG results, MOAA/S, CADSS and C-SSRS. Independent site raters for the MADRS, [redacted] are not allowed to access or review participants safety records and, therefore, must not provide clinical care for participants. Clinical care of participants will be performed by the investigator or delegate at the study site who are not MADRS, [redacted] raters.

Whenever possible, all efforts should be made to use the same independent raters for the MADRS, [redacted] at each site to assess the same participant throughout the study. If this is not possible, review of the appropriate prior assessments and communication with prior raters should be conducted, as needed. Any clinically relevant safety findings from the scales or the interviews must be communicated to the investigator.

During the study, the roles of the investigator and the independent site rater, including their back-ups, are not interchangeable at the participating sites.

8.3.2 Montgomery Asberg Depression Rating Scale (MADRS), SIGMA version

The Montgomery Asberg Depression Rating Scale (MADRS, SIGMA version) 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. In this study, the following recall periods will be used: “Last 7 days with euthymic baseline”, “over the past 4 hours”, "Last 7 days", and "Since last evaluation" for the primary endpoint. Whenever possible, the MADRS should be administered by the same rater to assess the same participant throughout the study.

8.3.3 Appropriateness of efficacy assessments

The MADRS is a standard scale used for registration studies of depression. It is relatively quick to administer, 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 sensitive to change from treatment effects over time, and is considered a gold standard registration scale for depression.

8.4 Safety

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 AE section.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every week or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-2 Assessment Specification

Assessment	Specification
Physical examination	A complete PE 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. A complete PE will be at screening and end of study visits. Information for all PEs must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an AE.

Assessment	Specification
Vital signs	Vital signs will include the collection of body temperature (recorded in °C), BP and pulse measurements and respiratory rate. Body temperature can be otic or oral according to local practice, but the same type of measurement should be used for the same participant at every assessment. After the participant has been resting in supine position for 5 minutes systolic and diastolic BP will be measured using an automated validated device with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. BP will be measured following ECG measurements. Clinically notable values of BP or pulse (see Exclusion Criteria Section 5.2 and Section 3) need to be confirmed by a repeated measurement 2-5 minutes after the first measurement. In case of repeated vital assessments, the eCRF should contain all assessments at any time point (including screening, baseline and post-dose time points).
Height and weight	Height is obtained in centimeters (cm) and body weight is obtained in kilograms (kg) and rounded to the nearest 0.1 kg, and will be measured at screening and baseline. Weight is obtained in indoor clothing, without shoes, and repeated at baseline.

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. Clinically notable laboratory findings are defined in Appendix 1 (Section 16.1).

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.

Fasting considerations:

The participants must be fasting at screening in order to measure fasting glucose. In case the sample was not taken in a fasted state, a repeat sample should be taken at Day 1 after the

participant has been fasting overnight. For the subsequent visits, all participants must also be fasting overnight. If not, no repeat sample will be taken.

Table 8-3 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes), other (absolute value preferred and percent) and platelet count will be measured.
Chemistry	Albumin, alkaline phosphatase, total bilirubin, bicarbonate, calcium, Total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), chloride, creatinine (Glomerular Filtration Rate to be calculated based on the Cockcroft-Gault formula), creatinine kinase (CK), Gamma-glutamyl transferase (GGT), glucose (fasting), lactic dehydrogenase (LDH), phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, blood urea nitrogen (BUN) or Urea, uric acid, C-reactive protein (high sensitivity). 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 clinically relevant abnormal TSH value, additional evaluation will be performed (free triiodothyronine [fT3] and free thyroxine [fT4]).
Urinalysis	A midstream urine sample (approx. 30 mL) will be obtained, 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, urobilinogen, ketones, leukocytes and blood. If the dipstick result is positive for protein, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts. Furthermore the protein-creatinine ratio (PCR) and the albumin-creatinine ratio (ACR) might also be measured
Coagulation	Prothrombin time/International normalized ratio (PT/INR), Activated partial thromboplastin time (APTT)
Alcohol / Drugs of Abuse*	Breathalizer / Dipstick
Pregnancy Test and Assessment of Fertility	Serum / Urine pregnancy test (as outlined in Section 8.4.3)

* Since urine dipsticks are neither quantitative nor sensitive enough to detect the exact timeframe when a drug was used, if a urine dipstick result is positive for a drug(s) of abuse, the prohibited use (as defined in Section 6.2.1 and Section 6.2.2) should be further confirmed by the treating physician by means of a clinical assessment and data obtained from the participant or his/her relatives. The investigator judgment prevails in case of contradictory data or results.

8.4.2 Electrocardiogram (ECG)

Figure 8-1 Timing of study procedures

Full details of all procedures relating to the ECG collection and reporting are contained in the technical manual provided by the core laboratory.

ECGs must be recorded after the participant rests for 10 minutes, in supine position, to ensure a stable baseline and heart rate. Thereafter, three ECG should be taken at approximately 1 or 2-minutes intervals (i.e., in triplicate) with ECG machines supplied by the core laboratory. The

preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs. The Fredericia QT correction formula (QTcF) must be used for clinical decisions. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each participant.

Triplicate 12 lead ECGs are to be collected with ECG machines supplied centrally. The ECGs must be reviewed by qualified site personnel in the first instance (e.g., cardiologist at site) and transmitted to the vendor as soon as possible after finishing the examination, for central review. The results of the centrally assessed ECGs will be electronically transferred into the clinical database.

Any original ECG not transmitted to the vendor electronically should still be forwarded for central review. A copy of the ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site.

Clinically significant ECG abnormalities present prior to randomization should be reported on the Medical History CRF page. New or worsened clinically significant findings occurring after randomization must be recorded on the Adverse Events CRF page.

A monitoring or review process should be followed for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment (see also Section 10.2.3 for details).

8.4.2.1 Cardiac imaging - MRA (magnetic resonance angiography), MUGA (multiple gated acquisition) scan or echocardiogram

Not applicable

8.4.2.2 Cardiac enzymes

Not applicable

8.4.3 Pregnancy and assessments of fertility

Contraception

During the study, investigators should ensure that study participants are regularly reminded of the importance of complying with the highly effective method of contraception, as it is applicable to them.

Women of child-bearing potential (WOCBP), must use highly effective methods of contraception during dosing and for 1 week after stopping of investigational drug. For WOCBP, 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 investigational drug. 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 participants on the study the vasectomized male partner should be the sole partner for that participant.
- Use of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of an IUD or IUS, the device or system should have been placed and well tolerated by the patient for a minimum of 3 months before taking the study treatment

  Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception other forms of hormonal contraception are not allowed for the purpose of contraception.

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 ICF.

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 testing

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. In case of a positive urine pregnancy test at Baseline, study treatment must not be administered.

Serum pregnancy testing will be conducted, unless specified otherwise.

Refer to Section 10.1.4 for details on Reporting Pregnancy.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. 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:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, luteinizing hormone (LH) and follicle stimulating hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening.

8.4.4 Safety evaluations related to mechanism of action of MIJ821

To further assess safety events associated with the mode of action of MIJ821 in participants, the following assessments are to be conducted:

- CADSS
- MOAA/S
- Memory assessment using orientation questions

8.4.4.1 Clinician-Administered Dissociative States Scale (CADSS)

The CADSS is a questionnaire that assesses dissociative effects. Each item is scored from 0 to 4 and individual scores are summed to obtain a total score ranging from a minimum of 0 to a maximum of 92. The trained staff administering the scale will also note their subjective interpretation of the participant's mental status and overall wellbeing, and whether any findings could be related to study drug. In this study, the following recall periods will be used: "current".

The CADSS will be administered electronically by qualified site personnel according to Table 8-1.

8.4.4.2 Modified Observer's Assessment of Alertness/Sedation (MOAA/S)

The purpose of this scale is to assess participant responsiveness on a scale from 0 (= Does not respond to painful trapezius squeeze) to 5 (= Responds readily to name spoken in normal tone [awake]).

The MOAA/S will be administered electronically by qualified site personnel according to Table 8-1.

8.4.4.3 Memory Assessment using orientation questions

Memory gaps/amnesia are AEs of Special Interest (AESI). Memory Assessment using orientation questions will be assessed by qualified personnel according to Table 8-1.

Orientation questions will be asked to assess presence or absence of amnesia, as well as any distress for the participant, at defined intervals. The outcome of this assessment will only be captured in the eCRF if amnesia is assessed as an AE. In that case, the onset and resolution of amnesia should be identified as precisely as possible and these data will be recorded in the eCRF. While definite amnesia must be reported as an AE in the eCRF, possible mild amnesia may or may not be reported as an AE based on investigator judgment.

8.4.5 Oxygen saturation

Pulse oximetry will be used to measure arterial oxygen saturation during the 4-hour observation period on the dosing day. The device will be attached to the finger, toe, or ear before study drug administration. Then, oxygen saturation will be monitored and documented in the source documents at site. Any arterial oxygen saturation (SpO2) <93% should be confirmed by an additional measurement on another part of the body. On the day of study drug administration, pulse oximetry will be recorded every 15 minutes starting from pre-dose until 4 hours post-dose. If oxygen saturation levels are <93% at any time during the 4 hour postdose interval, pulse

oximetry will be recorded every 5 minutes until levels return to ≥ 93% or until the participant is referred for appropriate medical care, if clinically indicated.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are standard for the study population and compounds with similar mechanism of action. As explained in Section 4.1.3, the safety assessments and their frequency were selected based on the completed FIH and PoC studies and the ongoing SAD study with s.c. MIJ821 in HVs.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, COA data may be collected remotely.

8.5.1.1 Clinician Reported Outcomes (ClinRO)

ClinROs will be used to establish the diagnosis of depression and to assess and record the patient's treatment history at Screening. They will also be used to measure the impact of MIJ821 on suicidality and disease severity with the following tools:

- SCID-5
- MGH-ATRQ
- C-SSRS
- [redacted]

Structured Clinical Interview for DSM-5 (SCID-5)

The SCID-5 is a semi-structured interview guide for DSM-5 disorders. It is administered by qualified personnel who are familiar with the DSM-5 classification and diagnostic criteria. The version used for this trial is the SCID-5-Clinical Trials version (SCID-5-CT). It guides the clinician step-by-step, through the DSM-5 diagnostic process, and allows to assess whether the diagnostic criteria have been met. Interview questions are provided along each corresponding DSM-5 criterion, which aids in rating each criterion as either present or absent. The SCID-5-CT covers the DSM-5 diagnoses most commonly seen in clinical settings.

The SCID-5-CT will be administered at screening only, as indicated in the Assessment Schedule Table 8-1. The SCID-5-CT responses will be recorded as source documentation only and will not be entered in the database.

Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ)

The MGH-ATRQ examines the adequacy of duration and dose of prior and current antidepressant treatments in a step-by-step procedure (Chandler 2010). When assessing the duration and dose of antidepressants, the examiner must always inquire about adherence to each treatment. In addition, the MGH-ATRQ assesses the degree of improvement on a scale from 0% (not improved at all) to 100% (completely improved).

The MGH-ATRQ will be administered at screening. Treatments with a response of "less than 25% improved" will be considered failed treatments. All treatments (failed and successful) used in the current episode for each participant should be listed on the MGH-ATRQ and entered in the corresponding CRF page. All treatments listed on the MGH-ATRQ and on-going at the time of screening should also be entered in the Concomitant Medication CRF page.

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The C-SSRS will be administered as defined in Section 8. In this study, the following recall periods will be used: "one month/one year" and "since last evaluation". Further details on the C-SSRS procedure are given in Section 10.2.4.

[redacted]

[redacted]

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 central laboratory manual 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.

In case of unscheduled visits for safety monitoring purposes during the time period from 4 h to 24 h after injection, unscheduled PK samples may be collected if operationally feasible.

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

Pharmacokinetic analytical method(s)

Concentration in plasma of MIJ821 will be determined by validated LC-MS/MS method. The lower limit of quantification (LLOQ) of MIJ821 in plasma is considered to be 0.1 ng/mL. Concentrations will be expressed in mass per volume units. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report. Samples collected from placebo-treated participants will not be measured.

[redacted]

Pharmacokinetic parameters

The following PK parameters of MIJ821 will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8 or higher):

- primary PK parameters: AUClast, Tmax, and Cmax
- secondary PK parameters: if data permit, additional PK parameters will be estimated e.g. T1/2, Area Under the Curve from time zero to infinity (AUCinf), AUC0-t (if needed, time range to be defined during PK analysis), CL/F, Vz/F (data not limited)

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal elimination phase for the potential determination of T1/2 will include at least 3 data points after Cmax. If the R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported of PK parameters depending on the estimation of the terminal elimination phase (e.g. CL/F, Vz/F, AUCinf).

[redacted]

[redacted]

8.5.4 Other Assessments

Local tolerability assessment

Local tolerability of the injection site will be assessed by clinical evaluation by the investigator or delegate of the following parameters:

- Erythema/redness
- Induration/swelling
- Ecchymosis/bruising
- Pain

The presence of erythema, induration and ecchymosis will be evaluated visually. If the size of any of these abnormalities is above 2.5 cm, the exact size of the lesion must also be measured.

The lesion size will be estimated and recorded as the largest diameter of the best fitted ellipsoidal form. Lesions will be graded as described below and recorded in the eCRF:

- Mild lesion: 2.5-5 cm
- Moderate lesion: 5.1-10 cm
- Severe lesion: >10 cm

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

This is a single dose study, therefore treatment discontinuation for the individual participant is not applicable.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops further protocol-required assessments or follow-up.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

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

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study stopping rules

Not applicable.

9.4 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their End of Study 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.

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. Documentation of attempts to contact the participant should be recorded in the source documentation.

9.5 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 participants 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 participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. 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 participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

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 clinical investigation participant 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 participant and identifying AEs.

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

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

AEs must be recorded 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 severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study 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 participant
3. Its duration (start and end dates or ongoing) and the outcome 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/permanently discontinued

6. Its outcome: recovery status or whether it was fatal

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

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 until EOS visit.

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 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 participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Dissociation and amnesia

Dissociation means a lack of connection within or between oneself and one's environment. It is not the same thing as "psychosis" which means fixed false beliefs (delusions) or false sensory experiences (hallucinations) but can be compared to the normal cognitive process of dreaming, where one is disconnected from one's body and the real world. Déjà vu and déjà entendu are classic dissociative experiences.

The two main forms of dissociation are depersonalization and derealization. In depersonalization one feels disconnected from oneself, whereas in derealization one feels disconnected from the world. This experience often is described as a sense of unreality, as if there was a film between oneself and one's experience of the world. Dissociation is not the same as a hallucination, as there is no false sensory experience (e.g., hearing voices that do not exist). Rather normal sensory experiences occur as if they are not fully normal, as if there is some disconnection between the observer and the objects experienced. Depersonalization in

extreme cases may involve a feeling that one's self is not one's self, or that perhaps multiple selves can be identified in oneself. Dissociation can affect cognitive processes. One's memories are not false, but they are remembered as if they are somehow not completely real. In severe cases, actual events may be forgotten.

Amnesia means loss of memory. Dissociative amnesia means that things are not remembered because of dissociation, i.e., because of a sense of lack of connection between the self and the world. All other types of amnesia occur in settings where there is no dissociation.

In assessing dissociative AEs or cognitive AEs of interest (such as amnesia or sedation), these AEs of special interest will be described in detail by participants and Investigators in writing in the source documents. The reported term should be as specific to the participant's experience as possible. Investigators will record carefully the onset and resolution time of such AEs. Safety scales should be more frequently administrated every hour for the first 4 hours since the start of the event.

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 participant 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 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 of TRD
    - 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 participant'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 participant 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 participant 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).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

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 participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until EOS visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than 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. Information about all SAEs is collected and recorded on the electronic Serious Adverse Event (eSAE) with paper backup SAE Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAE reporting timeframes:

1. SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
2. Randomized or Treated Participants: SAEs collected between time participant signs ICF until EOS visit.

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 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 EOS visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant 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.

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

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

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, participant 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 recorded on the appropriate CRF 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 Dosing CRF (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 the respective sections (Section 10.1.1and Section 10.1.2).

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant 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.

Please refer to Table 16-2 in Appendix 2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-2 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 16-3. Repeat liver chemistry tests (i.e. 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 participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

- If the initial elevation is confirmed, close observation of the participant will be initiated.
- Hospitalization of the participant 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
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

- Exclusion of underlying liver disease, as specified in Appendix 2 (Section 16.2)
- Imaging such as abdominal ultrasound, computerized tomography, or magnetic resonance imaging, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

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

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
  - 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, Urinary Tract Infection (UTI), extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Appendix 3 (Section 16.3).

Every renal laboratory trigger or renal event as defined in Table 16-5 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-6.

10.2.3 Cardiac Monitoring

To ensure participant safety cardiac monitoring has to be followed for all participants.

Please refer to Section 16.4 and Table 16-1 for clinically notable vital signs and ECG alert threshold values.

Post dose cardiac monitoring:

Every clinically significant cardiac event should be followed up by the investigator or designated personnel at the trial site, as summarized below.

- If the initial abnormality is confirmed, close observation of the participant can be initiated based on investigator's discretion
- Causality assessment of the cardiac event should be evaluated
- Thorough follow-up of the cardiac event. These investigations can include based on investigator's discretion: increasing the cardiac monitoring level; initiating additional diagnostic or therapeutic procedures to ensure patient safety, and to better characterize the finding and/or its cause; consultancy with a cardiologist
- Hospitalization of the participant if appropriate

Post dose QT prolongation:

In case of a clinically significant postdose QT prolongation, in addition to the abovementioned cardiac monitoring measures, the following additional measures are recommended

- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study treatment.

Post dose blood pressure monitoring:

The following monitoring criteria based on post-dose blood pressure assessments during the dosing phase should be followed:

At 1.5 hours post-dose, if the SBP is ≥160 mmHg and/or the DBP ≥100 mmHg, assessments should continue every 30 minutes until:

- The blood pressure is <160 mmHg SBP and <100 mmHg DBP, or
- In the investigator's clinical judgment, the subject is clinically stable or
- The subject is referred for appropriate medical care, if clinically indicated
- If the blood pressure remains ≥ 160 mmHg SBP and/or / ≥100 mmHg DBP, 4 hours after dosing, the subject should be referred for immediate medical treatment.

For participants with SBP ≥180 mmHg but <200 mmHg and/or the DBP is ≥110 mmHg but <120 mmHg participant should be referred to a cardiologist, or other specialist for a follow-up assessment.

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

10.2.4 Prospective suicidality assessment

The C-SSRS is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The C-SSRS must be administered as defined in the Visit schedule (Section 8).

The C-SSRS, which uses a semi-structured interview to probe participant responses, will be administered by an individual who has received training and certification in its administration. At the first study visit, the "baseline/screening" version of the C-SSRS will be administered. This version assesses suicidal ideation and suicidal behavior during the participant's last one year and during a predefined period of one month. At subsequent visits, the "since last visit" version will be administered.

If, at any time after screening and/or baseline (i.e., prior to randomization), the score is "yes" on item 4 or item 5 of the suicidal ideation section of the C-SSRS or "yes" on any item of the suicidal behavior section, the participant should be screened failed and adequate treatment and management should be provided as per standard of care.

In addition, all life-threatening events must be reported as SAEs. For example, if a participant answers "yes" to one of the questions in the suicidal behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the suicidal behavior section) should be reported as AEs and assigned the appropriate severity grade.

10.2.5 Adverse events of special interest

Based on the current available information, considering the ketamine safety profile and clinical/non-clinical evidence available for MIJ821, following events are considered AESI. This information is subject to change, based on the availability of incremental clinical experience with MIJ821. Please refer to the current Investigator Brochure for the most updated information on safety profile.

- Dissociation
- Sedation
- Cardiovascular effects (BP changes and QT interval prolongation on ECG)
- Respiratory effects (difficulty in breathing, changes in oxygen saturation)
- Suicidality (suicidal ideation or behavior)
- Memory gaps/ amnesia
- Cystitis or lower urinary tract adverse events

The list of current adverse events of special interest is available in the IB.

Post dose observation / Hospitalization

A four-hour post-dose observation period is implemented in this trial to ensure patients' safety and give required time for the potential events of interest to onset. Most of the events of interest should also be resolved by the end of the suggested observation period. The adverse events of interest should be followed up on site until resolution or until absence of safety risk assessed by the investigator based on clinical evaluation and judgement. If severe dissociative, psychotic, suicidal, sedative, cardiovascular or agitated symptoms emerge, it is recommended investigators hospitalize participants until those adverse events are resolved. If they persist, or based on clinical judgment or patient preference, those participants can be discontinued from the study at any time.

In case of a safety concern or worsening of depressive symptoms including suicidal ideation, participants' hospitalization should be prolonged or they can be re-hospitalized at any timepoint of the study overnight or for a longer period until they improve clinically, as per investigator clinical judgement. 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 mentioned monitoring period following the intravenous infusion, investigators must hospitalize participants 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 participant to leave the clinical setting, but in that case arrangements should be made such that family members or friends are present with the participant for at least 24 hours. If such arrangements cannot be made, it is recommended that the participant is hospitalized at least overnight.

Caution with performance of potentially dangerous tasks

Given that MIJ821 may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, participants should be advised about these potential risks. If the participant is feeling drunk or dizzy or if he/she experiences visual disturbances, hallucinations, or euphoric mood, then he/she should not drive, use machines or perform any other tasks that require his/her attention and good coordination.

In case of a safety concern, the participant should be hospitalized (or hospitalization should be prolonged) as per investigator's judgement until resolution of these events or absence of a safety risk.

Scales / tools to assess CNS related AEs

Additional scales have been implemented to assess events of sedation (MOAA/S), dissociation (CADSS) and C-SSRS scale will be used for assessment of suicidality. Investigators will be trained specifically on identification and appropriate recording of amnesia. Diagnosis of amnesia will be sought by detailed clinical evaluation of the participants (e.g. orientation questions, memory assessment questions, exclusion of other diagnosis, in conjunction with dissociation, categorisation of retrograde or anterograde amnesia, time to onset and time to resolution). In case of clinically significant findings or changes observed during the administration of the scales, it is recommended that an adverse event or SAE be recorded as appropriate.

See also sections Section 6.2.3, Section 9.1.1, and Section 10.2.4 for additional details.

Cardiovascular AEs

For cardiovascular effects, specifically for blood pressure increase, unless clinically indicated, it is recommended that transient increases in blood pressure not be treated, as the blood pressure typically returns to pre-dose values in 3-4 hours. In case of clinically notable values for vital signs as defined in Section 16.1, a treatment may be considered as per clinical judgement of the investigator. See also Section 10.2.3 for additional guidance.

10.3 Committees

10.3.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, review unblinded safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

The study may be put on hold and no further enrollment will take place pending full safety data review in case any significant safety finding(s) are observed by the DMC. In case of the study being put on hold, Novartis will promptly notify all concerned investigators/institutions, Ethics Committees/Review Boards and the Regulatory Authorities. The findings and the recommendations of the DMC will be documented and will be made available in the respective Ethics Committees/Review Boards and the Regulatory Authorities.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.3.2 Steering Committee

The Steering Committee (SC) is established as a group of external experts in the fields of psychiatry with profound knowledge and experience including clinical research in major

depression. These experts may participate in this trial as investigators, but will not be members of the DMC and Novartis representatives from the Clinical Trial Team (CTT).

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the CTT, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source

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

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, 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 participant 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 World Health Organization (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.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT 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/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis 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 participant 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/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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant).

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 participants will be disclosed.

12 Data analysis and statistical methods

The primary analysis will be performed at the End of Study. The efficacy will be tested and the dose-response relationship will be established based on the primary estimand by method of Multiple Comparison Procedure-Modeling (MCP-Mod).

Summary statistics will be presented by treatment group unless otherwise specified. For continuous variables, summary statistics will generally include: n, mean, standard deviation (SD), median, quartiles, minimum and maximum. For categorical variables, this will generally include: frequency and percentage in each category. Further technical details and discussions of statistical considerations will be provided in the Statistical Analysis Plan (SAP).

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all randomized participants who received a dose of the randomized treatment. Participants will be analyzed according to the study treatment received.

The Safety Set includes all participants who received any study drug. Participants will be analyzed according to the study treatment received.

The PK analysis set will include all participants with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

12.2 Participant demographics and other baseline characteristics

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

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 and combined by system organ class and by treatment.

12.3 Treatments

The Safety set will be used for the analyses below.

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

Concomitant medications will be summarized according to the Anatomical Therapeutic Chemical (ATC) code, preferred term and treatment group. Prohibited and rescue medication will be analyzed similarly. Significant non-drug therapies will be summarized by SoC, preferred term and by treatment group.

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

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

12.4 Analysis supporting primary objectives

The primary clinical question of interest is: What is the effect of s.c. MIJ821 versus placebo in addition to SoC at 24 hours after the injection of the study drugs on change in depressive symptoms measured by MADRS total score in participants with treatment resistant depression (TRD), who have already failed to adequately respond to at least two conventional antidepressants, while accounting for intercurrent events (IEs) with potential confounding effects and IEs leading to study discontinuation prior to 24 hours?

This section describes the primary analysis for the primary estimand. The related sensitivity analyses and supportive analysis will be detailed in the statistical analysis plan (SAP).

12.4.1 Definition of primary endpoint(s)

The primary estimand is described by the following attributes:

1. Population: participants with treatment resistant depression, who have failed to show adequate treatment response to at least 2 antidepressants previously.
2. Primary variable: change from baseline to 24 hours post dose in the MADRS total score
3. Treatment of interest: the randomized treatment (the investigational treatment MIJ821 or the placebo treatment) administered as a single s.c. injection on Day 1. The dose of the allowed concomitant medication (SoC) for depression must remain stable after baseline and during the trial.
4. Intercurrent Events (IEs) prior to MARDS assessment at 24 hours (see Section 12.4.3 for more details):

IEs with potential confounding effect prior to the 24-hour assessment:

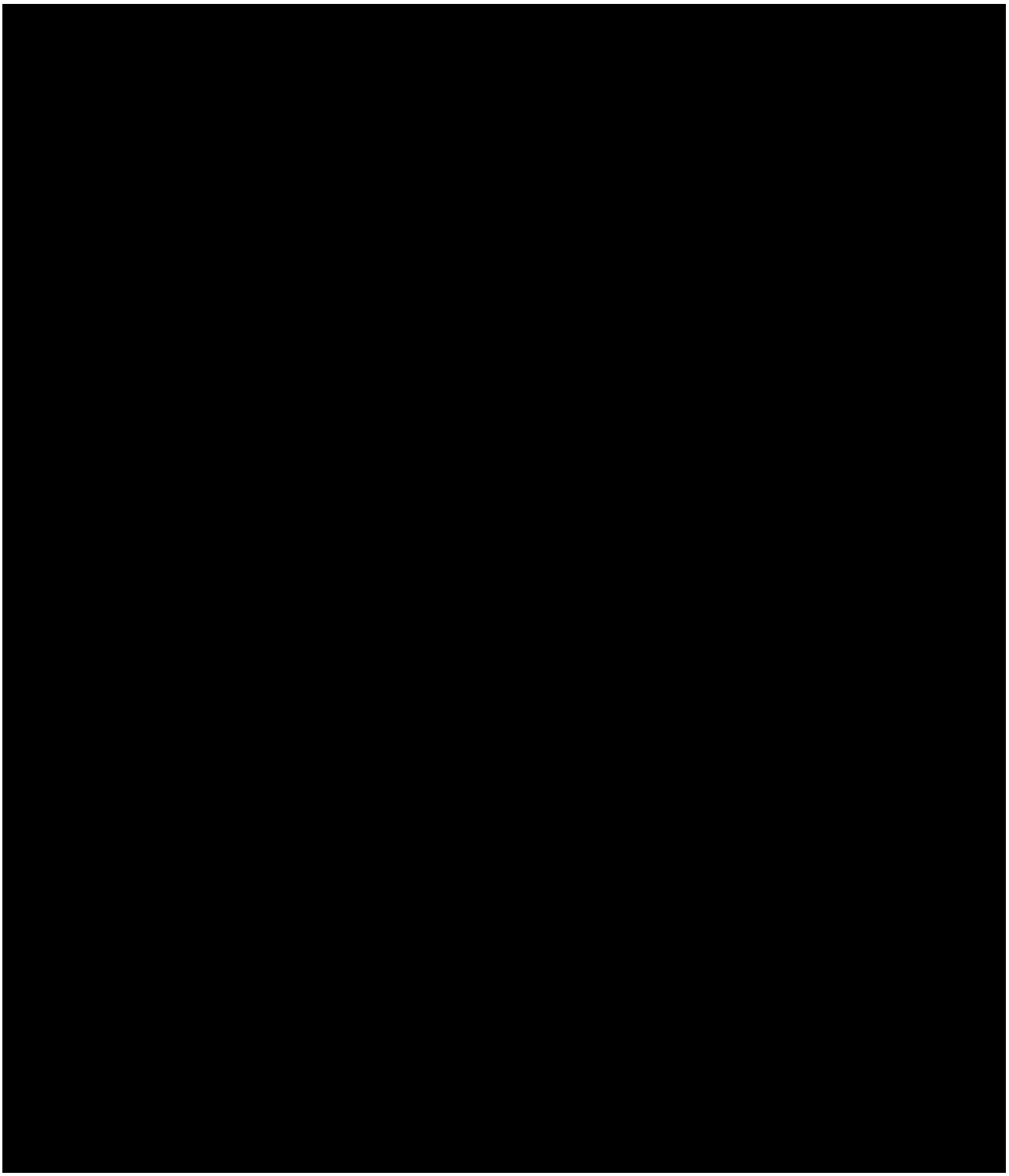
- New intake or change in concomitant medications/therapies which have a potential confounding effect
- Intake of prohibited medications/therapies
- Intake of rescue medication
- Pandemic related IEs

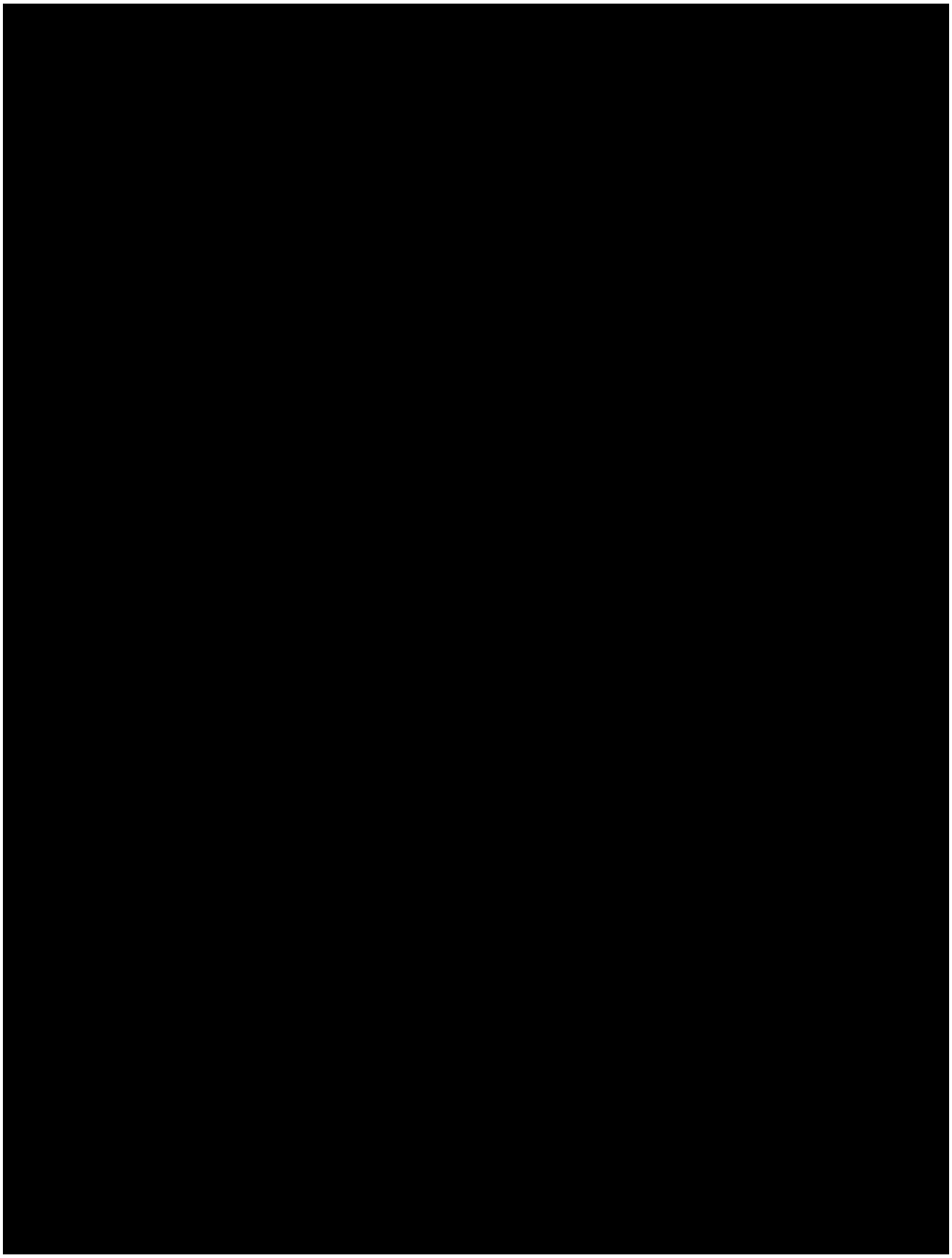
Participants who took prohibited medications/therapies, rescue medications, or took new or change concomitants medications/therapies which have potential confounding effect, will continue in the study and be assessed as scheduled.

IEs leading to study discontinuation prior to the 24 hour assessment:

- Adverse events (AE)
- Lack of efficacy (LoE)
- Other reasons for study discontinuation

The summary measure: treatment difference in variable means between study drug and placebo.





[redacted]

12.4.4 Handling of missing values not related to intercurrent event

Imputation of intermittent missing observations will be carried out following a MAR mechanism for all treatment arms.

[redacted]

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Duration of antidepressant effect of MIJ821

To assess the efficacy of antidepressant effect of MIJ821 over time, the following secondary endpoints will be evaluated:

- The change from baseline in the total MADRS score at Day 2, 8, 15, 22 and Day 29 visits after s.c. administration will be analyzed using the mixed-effect model for repeated measures (MMRM). This model will include the fixed, categorical effects of treatment, time (i.e. analysis visits), baseline MADRS score, class of anti-depressant standard of care, treatment-by-time and baseline MADRS score-by-time interactions. An unstructured (UN) covariance structure will be used to model the within-subject variability. More details of this analysis will be specified in SAP.
- Number (percentage) of participants who discontinued study due to lack of efficacy or need for new antidepressant treatment (pharmacological or psychotherapy) will be summarized by treatment arms.

Dose-response relationship of MIJ821

The assessment for the dose-response relationship of MIJ821 and estimation of the target dose will be based on the estimated dose-response curve derived from the MCP-Mod methodology in primary analysis (see Section 12.4.2).

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 adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period will be defined as starting from the date of administration of study treatment plus up to EOS visit.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the 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 adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and percentage) of psychotomimetic AEs (dissociation, amnesia, sedation) will be tabulated by treatment group, according to severity and relationship to drug.

The number (and percentage) of participants with adverse event of special interest (AESI) will be summarized by treatment. AESI include risks specified in the safety profiling plan or any other events of interest specific to the project.

A participant with multiple adverse events 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, participant, and visit/time and if ranges are available, abnormalities will be flagged.

Summary statistics will be provided by treatment group and visit/time. The average blood pressure change over time will be presented by line plot.

12-lead ECG

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

The overall interpretation of the ECGs will be summarized by treatment group and visit/time.

Any clinically significant changes in ECG parameters will be summarized by treatment group.

Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

Notable abnormal laboratory data will be listed by treatment group, participant and visit if ranges are available.

All laboratory data will be summarized by treatment group, 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.

12.5.3 Pharmacokinetics

MIJ821 plasma concentrations will be expressed in mass per volume. The plasma concentrations will be listed by treatment/dose, subject number, and visit/sampling time point. Descriptive summary statistics of plasma concentrations will be provided by treatment/dose and visit/sampling time point including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics of plasma concentrations will include arithmetic and geometric mean, SD, and CV and median, minimum, and maximum. Concentrations below

LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

PK parameters will be calculated as described in Section 8.5.2 and will be listed by treatment/dose and subject number. Descriptive summary statistics of PK pharmacokinetic parameters will be provided by treatment/dose. Summary statistics of pharmacokinetic parameters will include arithmetic and geometric mean, SD, and CV and median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

[redacted]

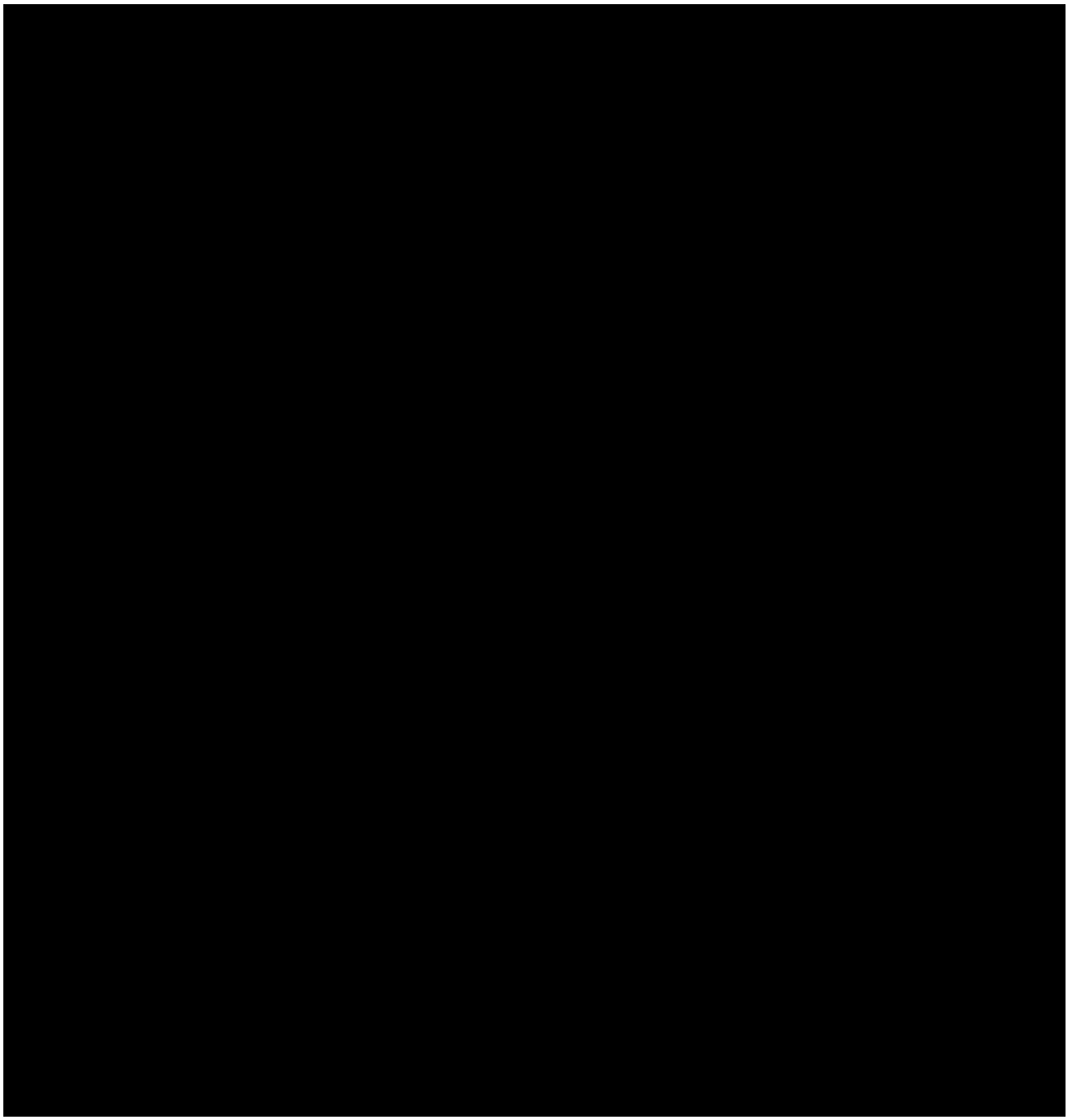
Table 12-2 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUC0-t	The AUC for the defined time period from 0 hour to time t.
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The total body clearance of bioavailable drug from the plasma (volume x time-1)
Vz/F	The apparent volume of distribution of bioavailable drug during terminal phase (associated with λz) (volume)

[redacted]

12.5.6 PK/PD relationships

The exposure response relationship will be presented graphically for PK exposure parameters (e.g. Cmax and AUClast) and the MADRS score change from baseline at 24 h after s.c. injection. Correlations will be assessed using statistical analysis methods (e.g. trendline analysis methods) or simple exposure response models (e.g. Emax models) if data allows. Details are described in the Statistical Analysis Plan.



12.8 Sample size calculation

12.8.1 Primary endpoint(s)

With the randomization ratio 1:1:1:1, the sample size of 14 per arm (placebo; MIJ821 1 mg; MIJ821 4 mg; MIJ821 10 mg) will provide approximately 90% power to detect a dose-response signal (i.e. to reject the null hypothesis of a flat dose-response curve where all MIJ821 dose means are equal to the placebo mean) with respect to change from baseline in MADRS at 24 hours post-dose using MCP-Mod methodology at the one-sided alpha = 0.05 level.

The six candidate DR curves (6 Sigmoid Emax) for power calculation are defined in Section 12.4.2. [redacted]

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, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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 participant 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.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter - at study completion/last visit
- Plain language trial summary - after CSR publication

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 participants 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 participant 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 participant 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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https://crediblemeds.org/

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Table 16-1 16-1 Clinically notable values for vital signs

Variable	Criterion value	Change relative to baseline
Heart rate/pulse	≥120 bpm; ≤50 bpm	increase of ≥ 15 bpm decrease of ≥ 15 bpm
Systolic blood pressure	≥180 mm Hg; ≤90 mm Hg	increase of ≥ 20 mm Hg decrease of ≥ 20 mm Hg
Diastolic blood pressure	≥105 mm Hg; ≤50 mm Hg	increase of ≥ 15 mm Hg decrease of ≥ 15 mm Hg

bpm= beats per minute

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-2 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers	● ALT or AST > 5 × upper limit of normal (ULN)
If ALT, AST and total bilirubin normal at baseline:	● ALP > 2 × ULN (in the absence of known bone pathology) ● Total bilirubin > 3 × 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 Total bilirubin > 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*
If ALT or AST abnormal at baseline:	● ALT or AST > 2x baseline or > 200 U/L (whichever occurs first)

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

Table 16-3 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	● Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms.
	If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)			
	If normal at baseline:	Normal	None	● Measure ALT, AST, ALP, GGT,

	ALT	TBL	Liver Symptoms	Action
	ALT > 5 x ULN for more than two weeks	For participants with Gilbert's syndrome: No change in baseline TBL		TBIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms. ● Initiate close monitoring and workup for competing etiologies.
	If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)			
	If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
	If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)			

Table 16-4 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Biliruin (isolated)		
>1.5 – 3.0 ULN	● Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution* to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	● Repeat LFT within 48-72 hours ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	● Hospitalize the participant ● Establish causality ● Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution* (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
Any AE potentially indicative of a liver toxicity	● Hospitalization if clinically appropriate ● Establish causality ● Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

* Resolution is defined as an outcome of one of the following: (1) return to baseline value, (2) stable value 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

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: 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.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-5 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 ³ 50 % +	● Consider causes and possible interventions ● Repeat assessment within 24-48h if possible ● Consider participant 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
New onset hematuria ≥ 3+ on urine dipstick	● 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

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

Whenever a renal event is identified, a detailed participant 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 edem
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine outpu

- 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 16-6 Follow-up of renal events

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 cell ● Blood pressure and body weigh ● Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric aci ● 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 participant 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 o ● 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

16.4 Appendix 4: ECG Alert Threshold Values

	Patients 18-30 years	Patients Adult > 30 years *
Resting heart rate Sinus rhythm [bpm]	HR < 30 and a HR decrease ≥ 25% HR > 130	HR < 40 and a HR decrease ≥ 25% HR > 120
QRS duration:		
=> No previous BBB **	> 120 and increase > 25% compared to (predose) baseline	> 120 and increase > 25% compared to (predose) baseline
=> Previous complete BBB * (>120 msec)	> 140 msec	> 140 msec
QTcF	QTcF > 500 msec QTcF increase > 60 msec ***	QTcF > 500 msec QTcF increase > 60 msec ***
Rhythm	Ventricular tachycardia	Ventricular tachycardia
Conduction	New complete heart block (Grade III AV block) Mobitz II AV block	New complete heart block (Grade III AV block) Mobitz II AV block
* Values displayed also correspond to Severe AE ** BBB = Bundle Branch Block *** Normal QTcF with QTc increase > 60 ms may indicate cardiac and non-cardiac pathology, e.g. hypothermia, new BBB, MI. cardiomyopathy or carditis.		

16.5 Appendix 5: Medications with a Known Risk of Torsades de Pointes

Table 16-7 Medications with a Known Risk* of Torsades de Pointes

Generic name	Brand name	TdP Risk
Aclarubicin	Aclacin and others	known
Amiodarone	Cordarone and others	known
Anagrelide	Agrylin and others	known
Arsenic trioxide	Trisenox	known
Astemizole	Hismanal	known

Generic name	Brand name	TdP Risk
Azithromycin	Zithromax and others	known
Bepridil	Vascor	known
Cesium Chloride	Energy Catalyst	known
Chloroquine	Aralen	known
Chlorpromazine	Thorazine and others	known
Chlorprothixene	Truxal	known
Cilostazol	Pletal	known
Ciprofloxacin	Cipro and others	known
Cisapride	Propulsid	known
Citalopram	Celexa and others	known
Clarithromycin	Biaxin and others	known
Cocaine	Cocaine	known
Disopyramid	Norpace	known
Dofetilide	Tikosyn	known
Domperidone	Motilium and others	known
Donepezil	Aricept	known
Dronedarone	Multaq	known
Droperidol	Inapsine and others	known
Erythromycin	E.E.S. and others	known
Escitalopram	Cipralex and others	known
Flecainide	Tambocor and others	known
Fluconazole	Diflucan and others	known
Gatifloxacin	Tequin	known
Grepafloxacin	Raxar	known
Halofantrine	Halfan	known
Haloperidol	Haldol and others	known
Hydroquinidine (Dihydroquinidine)	Serecor	known
Hydroxychloroquine	Plaquenil and others	known
Ibogaine		known
Ibutilide	Corvert	known
Levofloxacin	Levaquin and others	known
Levomepromazine (Methotrimeprazine)	Nosinan and others	known
Levomethadyl acetate	Orlaam	known
Levosulpiride	Lesuride and others	known
Mesoridazine	Serentil	known
Methadone	Dolophine and others	known
Moxifloxacin	Avelox and others	known
Nifekalant	Shinbit	known
Ondansetron	Zofran and others	known
Oxaliplatin	Eloxatin	known
Papaverine HCl (Intracoronary)		known
Pentamidine	Pentam	known
Pimozid	Orap	known
Probucol	Lorelco	known
Procainamide	Pronestyl and others	known
Propofol	Diprivan and others	known

Generic name	Brand name	TdP Risk
Quinidine	Quinaglute and others	known
Roxithromycin	Rulide and others	known
Sevoflurane	Ultane and others	known
Sotalol	Betapace and others	known
Sparfloxacin	Zagam	known
Sulpiride	Dogmatil and others	known
Sultopride	Barnetil and others	known
Terfenadine	Seldane	known
Terlipressin	Teripress and others	known
Thioridazine	Mellaril and others	known
Vandetanib	Caprelsa	known

* This is a non-exhaustive list, updated information are listed in www.qtdrugs.org

16.6 Appendix 6: Antidepressants recommended to be used as background therapy during the study

Generic Name
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)
Fluoxetine Fluoxetine delayed release
Paroxetine Paroxetine controlled release
Sertraline
SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)
Desvenlafaxine Desvenlafaxine Extended Release
Duloxetine
Levomilnacipran
Venlafaxine
NOREPINEPHRINE–DOPAMINE REUPTAKE INHIBITORS
Bupropion
SEROTONIN NOREPINEPHRINE RECEPTOR AGONISTS
Mirtazapine
SEROTONINE 2 ANTAGONIST/ REUPTAKE INHIBITORS
Trazodone*
MULTIMODAL ANTIDEPRESSANT/MULTIPLE SEROTONERGIC ACTIONS
Vilazodone
Vortioxetine
TRICYCLIC ANTIDEPRESSANTS
Amitripthyline*
Amoxapine
Desipramine
Doxepin
Imipramine
Nortriptyline*

Protriptyline
Trimipramine

Table adapted from FDA Approved Drugs to Treat Major Depressive Disorder (MDD). 2021

* Ensure that the prohibited time window before and after study drug injection is respected, as indicated in Table 6-2 (Prohibited Medications and Treatment)