NOVARTIS

Novartis Research and Development

MIJ821

Clinical Trial Protocol CMIJ821A12201 / NCT04722666

A double-blind, placebo-controlled, randomized dose-ranging trial to investigate efficacy and safety of intravenous MIJ821 infusion in addition to comprehensive standard of care on the rapid reduction of symptoms of Major Depressive Disorder in subjects who have suicidal ideation with intent

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AV block	Atrioventricular block
b.i.d.	bis in die/twice a day
[redacted]	
BDNF	Brain-Derived Neurotrophic Factor
BP	Blood Pressure
BPIC-SS	Bladder Pain/Interstitial Cystitis Symptom Score
BUN	Blood Urea Nitrogen
[redacted]	
CABG	Coronary Artery Bypass Graft
[redacted]	
CDS	Core Data Sheet
[redacted]	
CK	Creatinine Kinase
CL	Clearance
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CO	Country Organization
COA	Clinical Outcome Assessment
COVID	Coronavirus Disease
CQA	Clinical Quality Assurance
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTT	Clinical Trial Team
CV	Coefficient of Variation
[redacted]	
DBP	Diastolic Blood Pressure
DBS	Deep Brain Stimulation
DDI	Drug-Drug Interaction
DIN	Drug Inducted Nephrotoxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DR	Dose Response

DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
[redacted]	[redacted]
[redacted]	[redacted]
ECG	Electrocardiogram
EDC	Electronic Data Capture
EFD	Embryo Fetal Development
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trial Register
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiH	First-in-human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-Glutamyl Transferase
h	Hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
hsCRP	high-sensitivity C-Reactive Protein
i.m.	Intramuscular
i.v.	Intravenous
IB	Investigator's Brochure
ICD-10	International Classification of Diseases, tenth edition
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LPLV	Last Patient Last Visit
M.I.N.I.	Mini International Neuropsychiatric Interview
MADRS	Montgomery–Asberg Depression Rating Scale
MAOIs	Monoamine Oxidase Inhibitors

MAR	Missing At Random
MCP-Mod	Multiple Comparison Procedure-Modelling
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
[redacted]	[redacted]
NAM	Negative Allosteric Modulators
NMDA	N-Methyl-D-Asparate
NMDAR	NMDA Receptor
NOAEL	No Observed Adverse Effect
p.o.	oral(ly)
PCR	Protein-Creatinine Ratio
PD	Pharmacodynamic(s)
[redacted]	
PK	Pharmacokinetic(s)
PoC	Proof of Concept
PRN	Pro Re Nata
PRO	Patient Reported Outcomes
PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
R2 Value	Coefficient of Correlation
RBC	Red Blood Cell(s)
S-STS	Sheehan Suicidality Tracking Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
sCR	serum Creatinine
SD	Standard Deviation
[redacted]	[redacted]
SMQ	Standardized MedDRA Query
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SoC	Standard of Care
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TCA	Tricyclic Antidepressant
TEAEs	Treatment-Emergent Adverse Events
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
Vz	Apparent Volume of Distribution during Terminal Phase
WBC	White Blood Cell(s)
WoC	Withdrawal of Consent
WOCBP	Women of Childbearing Potential

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 (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Comprehensive Standard of Care (SoC)	Comprehensive SoC includes initial hospitalization and pharmacological SoC (antidepressant or antidepressant plus augmentation therapy)
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	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 patients 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.
eSource	eSource Direct Data Entry 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.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Independent site raters	The site raters administering the MADRS, [redacted]
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
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 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.
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
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
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
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
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)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 1 (01-Jun-2021)

Amendment rationale

This protocol amendment incorporates changes arising from Health Authorities feedback, revisions on inclusion/exclusion criteria with respect to patient weight, clarifications on the prohibited treatments (psychotherapy and medications) following input from investigators in participating countries.

After Health Authorities review of the protocol, selected inclusion and exclusion criteria have been revised to provide clarity (current contraindication versus prior history); or updated to align with the current product labelling medications in this class.

Following internal assessment, it was noted that infusion device compatibility studies performed to date do not cover the patients with body weight below 50 kg and above 120 kg (due to GMP qualification limitations). This information is already included in the Pharmacy Manual and has to be followed strictly. There patients outside the body weight range of 50-120 kg cannot be dosed at any dose level, thus not eligible for inclusion.

The use of rescue medications has been further specified to address health authority and investigator feedback. In addition, the list of prohibited medications has been updated to include medications commonly used in some participating countries in this patient population that have either an additive effect on cardiac safety.

The requirement of prohibiting changes to psychotherapy treatment was removed to align with clinical practice and facilitate recruitment of patients that receive psychotherapy at the time of study initiation.

Other clarifications to the protocol arising from health authority feedback are included in this amendment such as: [redacted]; inclusion of investigator guidance how patients will be managed after MIJ821 retreatment in the extension period; enhanced list of reasons of discontinuation by outlining the AEs of special interest and lack of efficacy; clarified that one course of treatment includes 3 infusions and only a single course of treatment is to be administered in the extension; clarified that unscheduled visits are to be performed in case of relapse.

[redacted]

The informed consent form has been updated to reflect the changes in this protocol amendment, as needed.

At the time of finalization of this protocol amendment no participant has been randomized in the study.

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 Protocol Summary and the List of Abbreviations have been updated for consistency with the main body of the protocol.
- Section 2 Objectives and endpoints
  - The scope of the primary objective has been clarified as it is only applicable to the Core period of the study.
  - [redacted]
  - [redacted]
  - [redacted]
- Section 3 Study Design
  - Addition of Figure 3-1 “Study Design” for clarity.
  - Overall Section 3.1, Section 3.2, Section 3.3 and Section 3.4 were reorganized to better describe the Core and Extension periods, the hospital discharge criteria, the responders/remitters definition, the relapse and the retreatment criteria.
- Section 3.2 Double-Blind Core Period Hospitalization and Hospital Discharge section
  - Clarification that a "Not at all" response corresponds to score 0.
  - Clarification that participants can be hospitalized at any time point as per clinical judgement.
  - Cross-reference to Section 10.2.5 about the risk related to dangerous tasks such as driving after study drug administration.
  - Move paragraphs “Criteria for Response and Remission” and “Criteria to enter the 52 weeks Extension Period” from Section 3.4 to Section 3.2
  - Removal of restriction related to psychotherapy.
- Section 3.3 Double-blind Extension Period
  - Added clarification that during the Extension Period, relapsing participant will not be allowed to be retreated if her/his weight is no longer within the allowed body weight range of 50-120 kg (inclusive).
  - Added more clarification that only one course of retreatment is allowed, cross-referenced to Section 6.1.4.

  - Addition of information about patient management after retreatment for relapses, cross-referenced to Section 3.4.
  - Update of Figure 3-2 "Study design in the extension in case of a relapse" to remove the 2 and 4 weeks follow-up visits after the treatment of relapse. Following completion of the course of retreatment, the participant will resume the 4 weekly follow-up visit schedule.
- Section 3.4 Criteria for retreatment in case of relapse
  - The title of this section has been adapted to match its content.
  - Clarification is added on patient management in case of clinical worsening and in case of second relapse.
  - Clarification that a scheduled and/or an unscheduled visit can be used to confirm a relapse.
- Section 5.1 Inclusion Criteria
  - Body weight range 50 to 120 kg (inclusive) has been added to inclusion criterion #2.
  - Clarification regarding the definition of participants having suicidal ideation with intent in the S-STS at baseline i.e. score (>0) has been added to inclusion criterion #5 (positive responses to Questions 3, and either 9 or 10).
- Section 5.2 Exclusion Criteria
  - Exclusion criterion #5 addition of the word "current" to borderline personality disorder.
  - Exclusion criterion #7 has been modified for clarity.
  - Exclusion criterion #11c related to prohibited psychotherapy has been removed.
  - Exclusion criterion #15 was modified to exclude participants in which the elevation of blood pressure or intracranial pressure as it may pose a serious risk.
  - The protocol text was adjusted to reflect the above clarifications in Section 3.2, Section 3.3, Section 4.1.2, Section 6.2.1, Section 6.2.2
- Section 6.1.4 Treatment duration
  - Clarification that only one course of retreatment is allowed in the extension Period.
- Section 6.2.1 Concomitant therapy
  - Addition of the latest simulation results on the predicted drug-drug interaction between MIJ821 and strong CYP2D6 inhibitors and information from the PoC study on co-medication was re-worded for clarification.
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action
  - Clarification that any benzodiazepines are allowed and addition of a table that lists examples of allowed corresponding maximum dose per day.
  - Clarification that the prohibited use of alcohol, cannabis or psychostimulants must also be assessed by a treating physician at the visit.
  - [redacted]
- Section 6.2.2 Prohibited medication

- Addition of amitryptyline, nortryptyline, quetiapine in Table 6-2 prohibited medications, given the potential additive risk of QT prolongation (risk of Torsades de Pointes), if taken concomitantly with the infusion.

- Section 6.2.3 Rescue medication
  - Addition of rescue medications, not only for agitation and anxiety but also in case of aggressive behaviour. Clarification for benzodiazepines and addition of antipsychotics. Cross reference for acute suicidality to the relevant protocol sections
- Section 6.3.2 Treatment assignment, randomization
  - Addition of a cross reference to Section 3.3 and Section 6.1.4 to clarify how to handle dose/dose regimen change at interim analysis
- Section 6.6.2 Recommended treatment of adverse events
  - Clarification that study drug treatment interruption or discontinuation applies to both Core and Extension
- Section 6.7.2 Instructions for prescribing and taking study treatment
  - Clarification that the dose calculation is based on the treatment arm and the patient body weight
  - Clarification that the protocol does not allow the re-treatment of participants in case of relapse if participants lose or gain weight and fall below 50 kg or above 120 kg.
- Section 7 Informed consent procedures
  - Addition of the consent for female partner into the list of informed consent procedures.
- Section 8 Visit schedule and assessments
  - Clarification that in case a visit is performed outside the schedule, subsequent visits shall be performed in accordance with the original visit schedule. In addition to scheduled visits, participants may have unscheduled visits as needed.
  - Tables 8-1 and Table 8-2: Respiratory rate was omitted in error, this is to be recorded as source data. It was also clarified in Table 8-3.
  - Clarification that pregnancy assessments are to be recorded as source data as described in Section 8.4.4, except at screening.
  - Table 8-1 and Table 8-2: Assessment of AESI Amnesia has been added in Assessment Schedules for clarity, as well as described in Section 8.4.5 and Section 10.2.5
  - 20 min safety monitoring was added into the Extension period in Table 8-2 to match the schedule of corresponding safety assessments in the Core Period
  - Table 8-2: Correction of the PK blood collection during the Relapse Retreatment phase. The PK blood collection that was placed at Day 2/24 hours has been removed and replaced by PK sample Day 1/ 4 hours post dose to be in line with the other measurements of the study.
- Section 8.2.1 Mini International Neuropsychiatric Interview (M.I.N.I.), Version 7.0.2
  - Wording clarifying the use of M.I.N.I. in the study has been added.
- Section 8.4.1 Laboratory evaluations
  - Addition of clarification on fasting condition for laboratory assessment.
  - Update of Table 8-4 to indicate that alcohol tests will be performed using breathalyzers.
  - Update of Table 8-4 footer to include clarifications regarding the use of the dipstick to confirm the presence of prohibited substances.

  - Add a footnote in Table 8-4 to clarify Cortisol is scheduled at same time point as Chemistry panel.
  - Add the reference of the Glomerular Filtration Rate formula.
- Section 8.4.3 Cardiac assessment
  - Addition of the need to mitigate the potential risk of self-harming attempts associated with the use of Holter wires.

[redacted]

- Section 9.1.1 Study treatment discontinuation and study discontinuation
  - Addition of lack of study treatment effect as a study treatment discontinuation reason
  - Clarification that study treatment discontinuation may occur in case of AESIs that indicate a safety risk to the participant
- Section 11.2 Database management and quality control
  - Clarification that all clinical scales administered by the clinician or self-reported by the participant will be collected on an eSource (Virgil® tablet) provided by the vendor who will also manage the database. The database will be sent electronically to Novartis with the exception of the audio recordings.
- Section 17 Appendix 6 Recall Periods
  - Revision of the recall period of several scales since the MADRS recall period is not validated beyond 7 days. [redacted] (S-STS, [redacted]
- 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	CMIJ821A12201
Full Title	A double-blind, placebo-controlled, randomized dose-ranging trial to investigate efficacy and safety of intravenous MIJ821 infusion in addition to comprehensive standard of care on the rapid reduction of symptoms of Major Depressive Disorder in subjects who have suicidal ideation with intent
Brief Title	Study of efficacy and safety of MIJ821 in addition to comprehensive standard of care on the rapid reduction of symptoms of Major Depressive Disorder in subjects who have suicidal ideation with intent
Sponsor and Clinical Phase	Novartis Phase 2b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The main purpose of this study is to support the dose selection for future Phase III clinical trials by evaluating efficacy and safety of four MIJ821 doses (0.0048, 0.016, 0.048 and 0.16 mg/kg) administered every other week by intravenous infusion on top of pharmacological antidepressant treatment, compared with placebo, for the rapid reduction of the symptoms of MDD in participants who have suicidal ideation with intent. In addition, the study will explore the effect of single dose administration of 0.16 and 0.048 mg/kg to treat MDD in participants who have suicidal ideation with intent. The study will also have a 12-month Extension Period to explore durability of the effect of the study treatment and the effect of MIJ821 on relapse rate, as well as safety of repeated MIJ821 administration.
Primary Objective(s)	The primary objective of this study is to investigate dose response relationship for 4 doses of MIJ821 vs. placebo in change from baseline in MADRS total score at 24 hours after the start of the first intravenous infusion. The primary clinical question of interest is: what is the effect of the MIJ821 versus placebo in change from baseline in MADRS total score at 24 hours post first dose administration, in conjunction with pharmacological standard of care (SoC), in patients with MDD who have suicidal ideation with intent, accounting for intercurrent events (IEs) with potential confounding effects and IEs leading to study discontinuation prior to the 24 hours assessment.
Secondary Objectives	To assess safety and tolerability of MIJ821 To assess the effect of MIJ821 on sustained response and remission To assess MIJ821 pharmacokinetics in plasma
Study design	This is a multi-center, double-blind, placebo-controlled, randomized, parallel group dose-ranging study. The study will enroll approximately 195 participants presenting with MDD with suicidal ideation with intent. The study consists of a Screening Period (up to 48 hrs), a double-blind Core Period (6 weeks) and an Extension Period (up to 52 weeks) for participants meeting the criteria for relapse retreatment at the end of the Core Period .
Study population	Male and female participants, 18 to 65 (inclusive), diagnosed with MDD who have suicidal ideation with intent.
Key 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), body weight from 50 to 120 kg (inclusive) at screening 3. DSM-5 defined major depressive disorder (MDD) with a current major depressive episode (MDE) without psychotic features at the time of screening based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.), Module A (Major Depressive Episode) assessed at Screening 4. Participants must have current suicidal ideation with intent, confirmed by a "Yes" response to Question B3 AND either Question B10 or Question B11 obtained from the M.I.N.I. Suicidality, Module B (Suicidality) assessed at Screening 5. Current suicidal ideation with intent, confirmed by "Yes" (>0) response to Question 3 AND either Question 9 or Question 10 obtained from the S-SST at Baseline

	6. Montgomery-Åsberg Depression Rating Scale (MADRS) score > 28 at Screening and before randomization on Day 1 7. Participants 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 local treatment guidelines) during the trial duration 8. In the physician's opinion, acute psychiatric hospitalization is clinically warranted to treat the patient's condition, and the patient is either already in the hospital or agrees to be hospitalized voluntarily for the required per protocol period (duration is defined in Section 3)
Key Exclusion criteria	Participants meeting any of the following criteria are not eligible for inclusion in this study. 1. Any prior or current diagnosis of bipolar disorder, MDD with psychotic features, schizophrenia, or schizoaffective disorder as obtained from M.I.N.I., Module C (Manic and Hypomanic Episodes) and Module K (Psychotic Disorders and Mood Disorders with Psychotic Features) assessed at Screening 2. Patients with acute alcohol or substance use disorder or withdrawal symptoms requiring detoxification, or patients who went through detoxification treatment (inpatient or outpatient) within 1 month before Screening. M.I.N.I. Module I (Alcohol Use Disorder) and Module J (Substance Use Disorder, Non-Alcohol) should be conducted at Screening 3. Participant has a current clinical diagnosis of autism, dementia, or intellectual disability 4. History of seizures. Note: childhood febrile seizures are not exclusionary 5. Participants with current borderline personality disorder as obtained from M.I.N.I., Module Y (Borderline Personality Disorder) assessed at Screening. 6. Participants with suicidal ideation or behavior caused primarily by another non-MDD condition, as obtained from M.I.N.I., Module Z (Suicidality Disorders Classification Interview) assessed at Screening 7. Known worsening or new appearance of suicidal ideation or behavior during a prior treatment with ketamine or esketamine or within 2 months after last ketamine or esketamine administration 8. Active hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) or active COVID infection as per medical history and/or available medical records 9. History of hypersensitivity to the study drugs or its excipients or to drugs of similar chemical classes. 10.Participants taking medications prohibited by the protocol (see Section 6.2.2,Table 6-2) 11. Intake of the following medications: a. Esketamine or ketamine 2 months before Screening b. Monoamine oxidase inhibitors (MAOIs) 14 days before Screening 12. Cardiac or cardiac repolarization abnormality, including any of the following: a. History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment b. History of clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade 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 pre first dose on Day 1, or inability to determine the QTcF interval 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: a. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome b. Concomitant medication(s) with a "Known Risk of Torsades de Pointes" that cannot be discontinued or replaced by safe alternative medication 7 days prior to Screening and during the Core. 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 any past history of hypertensive crisis, or participants in which the elevation of blood pressure or intracranial pressure poses a serious risk e.g. subjects with aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels); subjects with history of intracerebral haemorrhage 16. 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, impede compliance or hinder completion of the study.

	17. Have evidence of significant renal insufficiency, indicated by an estimated glomerular filtration rate (eGFR) of < 40 mL/min/1.73 m^2 at Screening 18. Use of other investigational drugs within 30 days of Screening 19. Pregnant or nursing (lactating) women 20. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 1 week after stopping study treatment (in the Core and Extension in case of retreatment). 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. In addition, male participants must not donate sperm for the period specified above. 21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 1 week after stopping medication (applies to the Core and Extension at the time of retreatment). Highly effective contraception methods include: ● Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). 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). Oral contraception or systemic hormonal contraception (e.g. transdermal or implanted hormonal methods) is not allowed for the purpose of contraception. 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. Patients eligible to receive MIJ821 treatment for relapse in the Extension Period should not be pregnant prior to the start of the treatment (see also Section 8.4.4 for additional details).
Study treatment	● MIJ821 ● Placebo ● Pharmacological Standard of Care (SoC)
Efficacy assessments	● Montgomery Asberg Depression Rating Scale (MADRS), SIGMA version before and after each infusion and each visit time point in the Core and Extension Period.
Key safety assessments	● Adverse events ● Physical examinations ● Vital signs ● Laboratory evaluation including: hematology, chemistry, urinalysis, thyroid, cortisol, alcohol/ drugs of abuse, pregnancy test ● Oxygen saturation, respiratory rate ● Cardiac assessment including: 12-lead ECG and 25 hrs Holter.
Other assessments	● Pharmacokinetics: PK blood samples will be collected for analysis parameters of MIJ821 in plasma. [redacted]

Data analysis	The Multiple Comparison Procedure – Modelling (MCP-Mod) methodology will be employed to assess the primary objective: to investigate dose response (DR) relationship for different doses of MIJ821 vs. placebo in change from baseline in MADRS total score at 24 hours post first dose administration. The adjusted treatment means from the ANCOVA will be used to test the null hypothesis of a flat DR relationship for the primary efficacy endpoint at a one-sided significance level of 5% against the alternative hypothesis of a non-constant DR curve. Once the DR signal is declared, the DR curve will be estimated.
Key words	Depression, Major Depression Disorder, Suicide, Montgomery–Asberg Depression Rating Scale, MIJ821, Phase IIb, Neuroscience.

1 Introduction

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). Prevalence rates vary by age, peaking in older adulthood (above 7.5% among females aged 55-74 years, and above 5.5% among males (WHO 2017). When long lasting and with moderate or severe intensity, depression may become a serious health condition. It can cause the affected person to suffer greatly, be unable to work, maintain relationships and attend to self-care. In the most severe cases, patients may become hospitalized or attempt or commit suicide.

Major depressive disorder (MDD) is the psychiatric diagnosis most commonly associated with suicide. Close to 800,000 people die due to suicide every year worldwide. Suicide is the second leading cause of death in 15-29-year-olds (WHO 2020). Suicidal ideation is prevalent and appears to be a suicidal risk factor among psychiatric patients with MDD (McAuliffe 2002; Sokero et al 2003; Coryell and Young 2005). The time between the onset of suicidal ideation and suicide attempt is often very short and can be minutes or a few days (Deisenhammer et al 2009; Otsuka et al 2015), highlighting the need for urgent intervention and development of novel antidepressant therapies with a rapid onset.

Concerted efforts over the past 40 years have led to the introduction of safer, better tolerated, and easier-to-prescribe antidepressants, most notably selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Nevertheless, about 30 to 40% of patients with MDD fail to respond to first-line treatments including oral antidepressant medications of all classes (SSRIs, SNRIs, tricyclic antidepressants (TCAs, etc.) and psychotherapy (Rush et al 2006). In addition, the onset to treatment response, even when effective, often takes at least four weeks, leading to greater suffering, expenses, and suicidal risk. Consideration of electroconvulsive therapy (ECT) for acute treatment of severe depression when a rapid response is required, or when other treatments have failed is recommended, however ECT use is limited by significant adverse reactions such as seizure induction, cognitive deficits and memory loss, as well as additional interventional concerns, e.g. use of general anesthesia. Therefore, there remains an ongoing high need for rapid acting, either more effective or better tolerated treatments that can in an effective way interrupt a depressive episode, reduce suicidality, and also able to prevent future depressive episodes.

1.1 Background

Ketamine, which is an N-Methyl-D-Aspartate (NMDA) receptor antagonist, has been shown to be effective in MDD in off-label research. A clinical study completed by (Berman et al 2000) was the first double-blind placebo-controlled crossover trial to demonstrate rapid antidepressant effects of ketamine following a single dose (0.5 mg/kg infused over 40 minutes) in seven patients. After this initial study, additional trials showed a similar effect in patients with unipolar and bipolar depression, including treatment-resistance depression (TRD) (Zarate et al 2006; Zarate et al 2012; Diazgranados et al 2010; Lapidus et al 2014; Murrough et al 2013a; Murrough et al 2013b). Ketamine has also been shown to reduce suicidality (Katalinic et al 2013; Murrough et al 2015). SPRAVATO® (esketamine), a non-competitive NMDA receptor antagonist, is the first approved drug of this class for the treatment of TRD, and for the treatment of depressive symptoms in adults with major depressive disorder (MDD)

with acute suicidal ideation or behavior. While both ketamine and SPRAVATO® have demonstrated a certain level of efficacy and showed a rapid mode of action, their safety profile is not without adverse events that are meaningful for both patients and clinicians. Targeting a specific subset of NMDA receptor (NMDAR) is one approach to potentially mitigate adverse effects of NMDAR inhibition while retaining antidepressant efficacy.

Evidence suggests that the NR2B negative allosteric modulators (NAMs) MK-0657 (also known as CERC-301) and CP-101,606 have low frequencies of dissociative adverse events (Garner et al 2015; Pagnozzi et al 1995; Preskorn et al 2008). Although, the relative contribution of each individual subtype of NMDARs to the adverse effects of pan-NMDAR inhibition is poorly understood due to the lack of selective inhibitors for the various subtypes, taken together, this suggest that achieving a safe, yet rapid-onset antidepressant efficacy is feasible with a compound selectively inhibiting NR2B receptor.

MIJ821 is a highly potent, selective and reversible low molecular weight NR2B-NMDA receptor NAM. MIJ821 is intended to be studied as a short-term treatment over 6 weeks in conjunction with pharmacological antidepressant SoC treatment, for the rapid reduction of depressive symptoms in adult patients with MDD who have suicidal ideation with intent. This treatment approach is intended to allow these patients to rapidly achieve a significant improvement of their depressive symptoms, and suicidal ideation.

The primary pharmacological properties of MIJ821 were characterized *in vitro* and *in vivo* and established a pharmacological basis for the intended clinical use. The nonclinical safety profile of MIJ821 has been evaluated in rats and dogs using the intravenous (i.v.) route in safety pharmacology studies, in single dose neurotoxicity studies, and in repeated dose toxicity studies of up to 6 weeks of duration (twice weekly dosing). MIJ821 is not genotoxic and not phototoxic. In safety pharmacology, transient increases in heart rate were seen in dogs. MIJ821 affected the human ether-a-go-go-related (hERG) channel potassium current with an IC50 of 1.1 μM and a related free Cmax-based safety margin of 22-fold at the human dose of 0.16 mg/kg. MIJ821 did not induce neuronal vacuolation (“Olney lesions”) or neuronal necrosis. In pivotal repeat dose toxicity studies, MIJ821 was tolerated with no adverse effects. No observed adverse effect levels (NOAELs) were identified in pivotal studies leading to AUC safety margins of 14-/32-fold (rats/dogs), when compared with human exposure at 0.16 mg/kg.

MIJ821 has been studied in a first-in-human (FIH) study in healthy volunteers (Study CMIJ821X2101) and in a Proof of Concept (PoC) study in patients with TRD (CMIJ821X2201). Both studies have been completed. Overall, the totality of the safety data suggests that MIJ821 was well tolerated. Additionally, in TRD patients participating in the PoC study, significant improvement on MADRS score at 24 h was reported and sustained improvement was seen over 6-weeks of treatment for all dose groups. MIJ821 was effective at all time points, especially in the lowest dose (i.e. 0.16 mg/kg every week or every other week).

In summary, the available preclinical and clinical data, MIJ821 mechanism of action, and available safety information, combined with the potential of MIJ821 to effectively treat depressive symptoms in patients suggests a favorable risk-benefit ratio and supports this Phase 2b dose ranging study.

1.2 Purpose

The main purpose of the study is to support dose selection for future Phase 3 clinical trials by evaluating the efficacy and safety of four MIJ821 doses (0.0048, 0.016, 0.048 and 0.16 mg/kg) administered every other week by intravenous infusion on top of pharmacological antidepressant treatment, compared with placebo plus pharmacological antidepressant treatment, for the rapid reduction of the symptoms of MDD in participants who have suicidal ideation with intent. In addition, the study will explore the effect of single dose administration of MIJ821 0.16 and 0.048 mg/kg to treat MDD in participants who have suicidal ideation with intent.

The study will also have a 12-month Extension Period to explore durability of the effect of the study treatment and the effect of MIJ821 on relapses rate, as well as safety of repeated MIJ821 administration.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Core :** To investigate the dose response relationship for 4 doses of MIJ821 vs. placebo	• Change from baseline in MADRS total score at 24 hours after the start of the first infusion
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Core:** To assess safety and tolerability of MIJ821	• Number and severity of treatment-emergent adverse events (TEAEs), including AEs of special interest in the Core Period
• **Core and Extension:** To assess the effect of MIJ821 on sustained response and remission	• Proportion of participants meeting response criteria (≥50% reduction from baseline in MADRS total score) over time in the Core Period. Proportion of participants meeting criteria for sustained response (≥50% reduction from baseline in MADRS total score sustained for a period of at least four weeks) in the Core Period Proportion of participants meeting remission criteria (MADRS total score of ≤12) over time in the Core Period Proportion of participants meeting criteria for sustained remission (MADRS total score of ≤12 sustained for a period of at least four weeks) in the Core Period Proportion of participants meeting criteria for relapse over all randomized population over fixed period in the Extension Period Proportion of relapsing participants meeting response criteria or remission criteria after the first infusion of MIJ821 retreatment in the Extension Period
• **Core and Extension:** To assess MIJ821 pharmacokinetics in plasma	• PK parameters of MIJ821 in plasma after 1st infusion described by AUClast, Cmax, Tmax (parameters not limited) and after each infusion described by Cmax and Tmax.

Objective(s)	Endpoint(s)
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	

2.1 Primary estimands

The primary clinical question of interest is: what is the effect of MIJ821 versus placebo in conjunction with pharmacological standard of care (SoC) on change from baseline in MADRS total score at 24 hours post first dose administration, in patients with MDD who have suicidal ideation with intent, accounting for intercurrent events (IEs) with potential confounding effects and IEs leading to study discontinuation prior to the 24 hours assessment.

Rationale

The justification for the primary estimand is that it will capture the effect of the study drug in addition to SoC, thereby mirroring conditions in clinical practice, and without confounding effects from intercurrent events on Day 1.

The primary estimand is described by the following attributes:

- Population: Patients with MDD who have suicidal ideation with intent. Further details about the population are provided in Section 5.
- Endpoint: change from baseline in MADRS total score at 24 hours post first dose administration
- Treatment of interest: the randomized treatment (MIJ821 0.0048 mg/kg, 0.016 mg/kg, 0.048 mg/kg, 0.16 mg/kg or Placebo, 40 min i.v. infusion) add-on to SoC. Dose titration or adjustments of SoC antidepressant treatment allowed during the first 2 weeks of double-blind treatment, if needed, with dosages maintained thereafter during the core treatment phase. Further details about the investigational treatment and control treatment are provided in Section 6.
- Handling of intercurrent events (IEs) prior to MADRS assessment at 24 hours (see more details in Section 12.4.3):
  - Intake or change in concomitant medications/therapies other than SoC which have potential confounding effects: hypothetical strategy
  - Intake of prohibited medications/therapies: hypothetical strategy
  - Intake of rescue medications: hypothetical strategy
  - IEs related to pandemic: hypothetical strategy
  - IEs leading to study discontinuation due to Adverse events (AEs), lack of efficacy or other reasons: treatment policy strategy

Further details about the concomitant treatment, prohibited treatment and rescue medication are provided in Section 6.

- The summary measure: difference in variable means between treatments

2.2 Secondary estimands

Not applicable

3 Study design

This is a Phase 2b double-blind, placebo-controlled, randomized, parallel-group dose-ranging trial to investigate the efficacy and safety of four doses of intravenous MIJ821 administered as a 40-min infusion in addition to comprehensive standard of care (SoC) for the rapid reduction of the symptoms of MDD in participants who have suicidal ideation with intent. Comprehensive SoC includes initial hospitalization and pharmacological antidepressant therapy (antidepressant monotherapy or an antidepressant plus augmentation). In addition, the study will also explore the effect for single dose administration of 0.16 mg/kg and 0.048 mg/kg given once to treat MDD in participants who have suicidal ideation with intent.

Participants meeting the eligibility criteria will be randomized in a 2:1:2:2:2:2:2 ratio to treatment with:

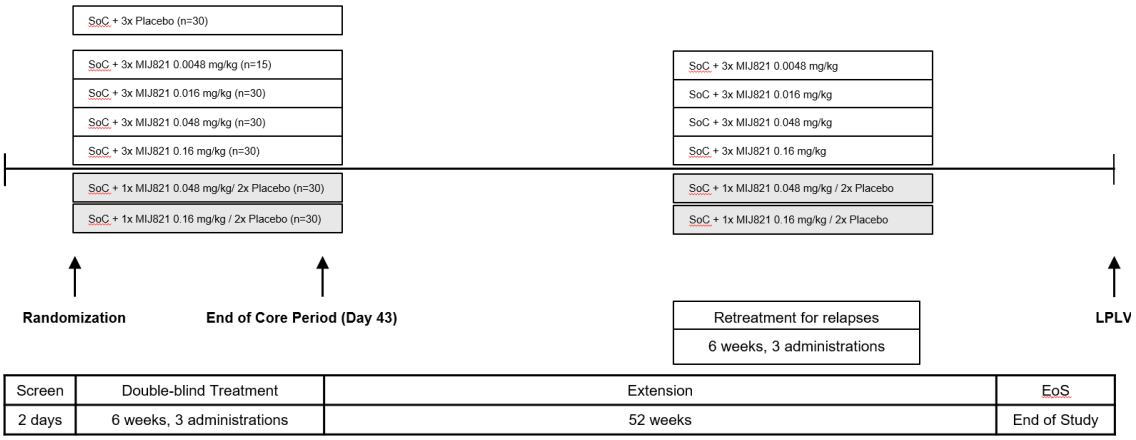
- placebo every other week
- MIJ821 0.0048 mg/kg every other week
- MIJ821 0.016 mg/kg every other week

- MIJ821 0.048 mg/kg every other week
- MIJ821 0.16 mg/kg every other week
- MIJ821 0.048 mg/kg single infusion with two subsequent placebo dosages given every other week
- MIJ821 0.16 mg/kg single infusion with two subsequent placebo dosages given every other week

On the top of ongoing pharmacological antidepressant SoC treatment. In all treatment arms, investigational treatment will be administered by intravenous infusion every other week, three infusions in total during the placebo-controlled double-blind Core, 6-week period of the study.

The study consists of three periods: a Screening Period (up to 48 hrs), a double-blind Core Period (6 weeks) and Extension Period (up to 52 weeks).

Figure 3-1 Study design



3.1 Screening Period

The Screening Period will start when the participant signs the informed consent form. The eligibility of the participant will be determined based on assessments performed at the Screening visit (up to 48 hrs) and also on Day 1 before randomization.

All participants must require hospitalization due to MDD with suicidal ideation with intent. Participants may have already been in the hospital prior to Screening or must agree to hospitalization at Screening.

All participants must receive pharmacological antidepressant SoC, which either has been initiated prior to the study entry or must be initiated or adjusted during the Screening Period, upon signing informed consent.

3.2 Double-blind Core Period

The double-blind Core Period starts on Day 1 and lasts 6 weeks. All baseline assessments (including the primary efficacy scale MADRS) must be performed on Day 1, prior to randomization. Investigational drug will be administered in a double-blind manner in the form

of a 40-minute intravenous infusion on Day 1, Day 15 and Day 29. Designated unblinded qualified site personnel is required for the preparation of the infusion prior to administration.

Hospitalization and hospital discharge

The first intravenous infusion on Day 1 must be performed in an inpatient setting and the participant should remain hospitalized for a recommended observation period of 72 hours (with shorter or longer hospitalization duration allowed if clinically warranted per local standard practice), and as long as required thereafter as per investigator's clinical judgment and/or local practice guidelines/recommendations. The minimum period of hospitalization is 24 hours after infusion on Day 1.

In case of a safety concern, worsening of depressive symptoms including suicidal ideation, participants can be hospitalized at any timepoint of the as per investigator clinical judgement (see details in Section 10.2.5).

When hospitalization is no longer required as per investigator's clinical judgment and/or local practices, and the participant meets the minimum protocol discharge criteria (defined below), the site personnel should ensure that participant continues visiting the study site for investigational treatment infusions (on an outpatient basis) and study assessments as per the visit schedule.

Participants must be observed for 4 hours after the start of each infusion both for inpatient and outpatient settings.

Any relevant safety events (e.g. sedation, dissociation, amnesia, blood pressure increase or clinically relevant ECG findings) during the 4-hour observation period must be monitored at site until resolution and/or absence of safety risk, as assessed by the investigator.

All patients who are ready for hospital discharge as per the investigator's clinical judgement must meet at least the following hospital discharge criteria as outlined below:

- [redacted]
- Absence of any safety risk assessed by the investigator based on clinical evaluation and judgement

Note, caution must be taken prior to discharging participants with depressive and/or suicidal symptoms, see detailed guidance in Section 10.2.5.

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 instructed to avoid such activities if the participant is feeling drunk or dizzy or if he/she experiences visual disturbances, hallucinations, or euphoric mood.

Standard of Care / psychotherapy

Dosage titration or adjustments of antidepressant pharmacological SoC treatment are allowed only during the first 2 weeks of double-blind treatment, as needed, with SoC dosages maintained thereafter during the Core Period.

Any kind of psychotherapy is allowed during the course of the trial

All participants must follow the visit schedule as defined in Section 8. At each scheduled visit, investigators/designated site staff should perform efficacy and safety assessments (refer to Table 8-1 Assessment schedule).

Response and remission criteria

Response is defined as a ≥ 50% reduction from the baseline MADRS score at any visit during the study.

Remission is defined as MADRS total score of ≤12 points at any visit during the study.

Criteria to enter the 52 weeks Extension Period

Participants who complete the Core Period on study treatment (with Day 29 infusion completed) and meet one of the below criteria at the End of the Core Period (Day 43) will continue in the 52 weeks Extension Period:

- ≥ 50% reduction from the baseline MADRS at the end of Core (Day 43) (participant is a Responder)
- MADRS total score of ≤12 points at the end of Core (Day 43) (participant is a Remitter)

Any worsening of depressive or suicidal symptoms during the Core Period is not considered a relapse. Participants who do not meet the criteria to continue in the 52 weeks extension will follow an abbreviated extension for 8 weeks and will be categorized as non- responder, or non-remitters, respectively.

3.3 Double-blind Extension Period

After completing the double-blind Core Period, all participants will enter the Extension Period for a minimum of 8 weeks and a maximum of 52 weeks.

Those participants who are not responders and not remitters at the end of the Core Period (see in this section, subsection Extension Follow-up duration for more details), will be observed in an abbreviated Extension Period lasting 8 weeks only to obtain safety data and evaluate withdrawal and rebound effects of MIJ821. Because those participants did not respond to the treatment as defined in Section 3.2 in the first instance, no retreatment will be provided in case of relapse. Those participants are allowed to adjust their SoC in their 8 weeks Extension Period, as necessary.

Study treatment

Participants who are classified as responders or remitters at the end of the Core Period (see Section 3.2 for more details), will be eligible to one retreatment course in case of a relapse

in the Extension Period , and should be observed for up to 52 weeks or clinical worsening after retreatment, whichever comes first (see in this section, subsection Extension Follow up Duration, and Section 3.4).

In the event of relapse (see Section 3.4 retreatment in case of relapse), participants will receive study treatment (called retreatment), as in the Core Period, in a blinded manner. All participants will be pre-randomized to relapse retreatment on Day 1 in the Core Period as described below:

- Participants who were receiving MIJ821 in the Core Period will be assigned to the same dose and regimen for the retreatment in case of relapse (if any in the Extension Period)
- Participants who were randomized to placebo in the Core Period will be assigned to one of the active treatment arms in the Extension Period (see Section 6.3.2)

After the dose and dose regimen for Phase 3 have been selected after the interim analysis, participants who relapse will receive the selected Phase 3 dose and regimen in a dose-blinded manner for the retreatment in case of relapse. Patients who have already started retreatment for the relapse will continue on the originally assigned dose.

Standard of Care

During the Extension Period, pharmacological antidepressant therapy can be modified only for non-responders or non-remitters. Those participants, who are classified as a responder or remitter at the End of the Core Period must maintain a stable SoC. In case of a relapse, the SoC pharmacological treatment can be adjusted, if needed, during the first 2 weeks of retreatment for relapse. Participants may or may not be hospitalized for the retreatment for relapse as per clinical judgment and local practices.

SoC can be adjusted or modified after the relapse retreatment, as clinically warranted. Extension Follow-up Duration

All participants must complete a follow-up period after the End of Core Period visit (Day 43):

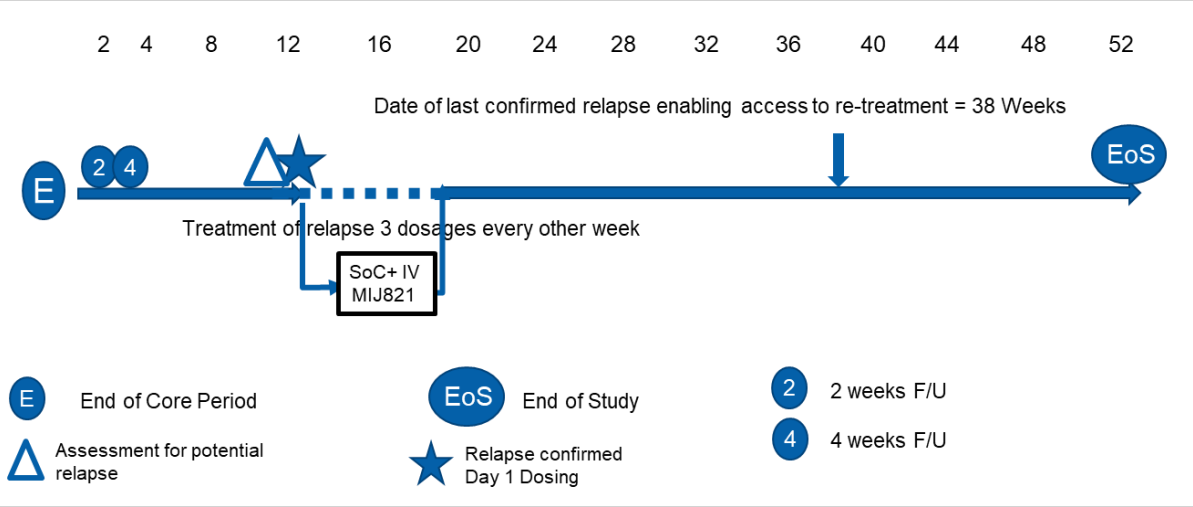
- For participants who are neither remitters nor responders at the End of Core Period (Day 43) Section 3.2, the follow up will last 8 weeks and consists of 3 mandatory visits (the 2 weeks Follow-up visit, the 4 weeks Follow up visit and the End of Study visit occurring 8 weeks after Day 43)
- For participants who are responders or remitters at the End of the Core Period (Day 43), and who do not experience any relapse, the Extension Period will last 52 weeks. This will consist of the 2 weeks Follow-up visit, the 4 weeks Follow-up visit, and thereafter Follow-up visits occurring every 4 weeks up to End of Study visit at Week 52
- Participants who are responders or remitters at the End of the Core Period (Day 43), and who relapse during the Extension Period, will receive one course of retreatment with MIJ821.
    - After that course of retreatment:
        - The participant will resume the 4 weekly Follow-up visit schedule (E.g., if the 6 weeks relapse retreatment period occurred from week 19 to 25, the participant will not perform visits week 20 and week 24, and will resume the follow-up at week 28).

- The duration of the follow up will be as per the initial schedule up to Week 52 or clinical worsening, whichever comes first, but they must complete at least 8 weeks follow-up period (see Section 6.1.4). Signs of clinical worsening may include worsening of depressive mood, need for SoC adjustments, a suicidal attempt, hospitalization for depression or suicidal ideation or behavior. For patient management see Section 3.4, subsection Relapse and Clinical Worsening.

- Participants who are responders or remitters at the End of the Core Period (Day 43), and who relapse during the Extension Period but do not meet the weight requirements of 50-120kg (inclusive), cannot be retreated for the relapse and must be discontinued. The Extension period for these participants should last at least 8 weeks before the discontinuation.

The total duration of the Extension Period is 52 weeks, maximum. Therefore, the last date of confirmed relapse enabling access to the retreatment period is 38 weeks. If a participant relapses on or after that date, the participant must complete the End of Study visit as soon as possible.

Figure 3-2 Study design in the extension in case of a relapse



3.4 Criteria for retreatment in case of relapse

Relapse and clinical worsening

A relapse manifests as the appearance of new depressive symptoms or worsening of previously stable or improving MDD symptoms. During the Extension Period, participants experiencing deterioration must be assessed by the treating physician and the relapse must be confirmed by assessment with MADRS during scheduled or unscheduled visit.

Signs of clinical worsening may include worsening of depressive mood, need for SoC adjustments, a suicidal attempt, hospitalization for depression or suicidal ideation or behavior.

Criteria for retreatment in case of relapse in the extension period

Meeting any of the following criteria will be considered a relapse and will be followed by a retreatment:

- MADRS total score ≥22 for 2 consecutive visits separated by 5-14 days AND meeting DSM-5 criteria for MDE (confirmed with M.I.N.I. Module A (Major Depressive Episode) to be eligible for relapse retreatment. The date of the first MADRS assessment will be the date of relapse. In addition, those participants who are responders at the End of Core period (≥50% improvement) but are not remitters (MADRS ≤12), should demonstrate ≥50% worsening from their MADRS total score reported at the End of Core Period (End of Core Visit).

OR

- Hospitalization for worsening depression or any other clinically relevant event suggestive of a relapse (i.e. suicide attempt, or hospitalization for suicide prevention) AND meet DSM-5 criteria for MDE (independently of the MADRS score; confirmed by M.I.N.I. Module A (Major Depressive Episode). The start date of hospitalization will be the start date of relapse. In case of a clinically relevant event, without hospitalization, the start date of the event will be used as the relapse date.

Because assessments for relapse need to occur at two consecutive visits separated by 5-14 days, scheduled visits and/or unscheduled visits can be organized. Relapse confirmation can be performed either at the Pre-retreatment visit or before the first infusion given for retreatment. If several relapse criteria are met, the first will be defined as the date of relapse.

In case of clinical worsening after participant already received one course of retreatment for relapse, the patient must be discontinued, as soon as 8 week follow up from the last dose of MIJ821 was administered. These patients will be managed according to investigator judgement with SoC that can be adjusted or modified after the relapse retreatment, as clinically warranted.

4 Rationale

4.1 Rationale for study design

The study design, patient population, background treatment (pharmacologic standard of care), endpoints, inclusion and exclusion criteria are aligned with regulatory guidelines such as the draft guidance for developing drugs for treatment major depressive disorder (FDA 2018) and EMA guideline for Clinical investigation of medicinal products in the treatment of depression (EMA 2013). This protocol was developed in consultation with EMA and FDA.

The choice of treatment duration and timing of assessment of primary and other endpoints is based on the MIJ821 rapid mechanism of action, as well as the expected onset and durability of the treatment effect as demonstrated in the proof of concept study in patients with treatment-resistant depression (CMIJ821X2201). The treatment resistant depression (TRD) population represents a subtype of the overall MDD population and, therefore, the safety and efficacy data obtained from the PoC study in TRD patients are generalizable to the overall MDD population including the targeted population of MDD patients with suicidal ideation with intent.

To ensure patient safety and to comply with clinical practice, the double-blind Core Period will be conducted first in an inpatient setting and later in an outpatient treatment setting, as appropriate. The Core Period includes a weekly visit schedule for efficacy assessment and safety monitoring.

To allow evaluation of durability of the initial response and the potential effect of MIJ821 on relapses long term, as well as to evaluate MIJ821 safety after a repeated use, a 12-month extension follows the 6 weeks Core Period.

4.1.1 Rationale for primary efficacy endpoint

According to FDA draft guidance for developing drugs for the treatment of major depressive disorder (FDA 2018) when compared to 6-8 weeks for antidepressants of established classes, for rapid-acting novel antidepressants, an earlier primary efficacy endpoint would be appropriate.

In the PoC study (CMIJ821X2201), MIJ821 demonstrated a compelling treatment effect compared to placebo for both doses tested at 24 hours post dose. Based on these data a 24 hour time point was chosen to assess the primary variable.

Based on the rapid mode of action of MIJ821, the primary efficacy endpoint of this study is to assess the treatment effect of an extended dose range for MIJ821 (4 doses) vs placebo at 24 hours after the first intravenous infusion of investigational drug.

The efficacy will be determined by using the MADRS (Montgomery and Asberg 1979) which is a gold standard scale for the evaluation of major depressive episodes and widely used for registration studies in depression.

4.1.2 Rationale for choice of background therapy

MIJ821 is intended as a short-term treatment to supplement SoC treatment in an emergency situation (patients with moderate to severe MDD who have suicidal ideation with intent). To ensure proper patient safety and to address the ethical concern of having patients on placebo with no treatment benefit, a pharmacological antidepressant background therapy as per local clinical practice and guidelines should be taken by all participants in the trial, on top of hospitalization (recommended period of 72 hours; with shorter or longer hospitalization duration allowed if clinically warranted per local standard practice, but not less than 24 hours) after the first study drug administration. To evaluate MIJ821 treatment in the appropriate context of SoC and because patients will be in an emergency situation, dosage titration or adjustments of standard-of-care antidepressant treatment will be allowed during the first 2 weeks of double-blind treatment, if needed, with dosages maintained thereafter during the Core Period. Psychotherapy is allowed.

In the Extension Period, pharmacological antidepressant therapy can be modified only for those participants who are not eligible for entering the 52 weeks Extension Period (see Section 3.2 for more details) to allow therapy adjustments required to treat the MDD condition as per local clinical guidelines and practices.

By contrast, participants who at the End of the Core Period are eligible for entering the 52 weeks Extension Period (see Section 3.2 for more details), will not be allowed to change their standard

of care treatment until a relapse since they have responded to the study treatment and need to continue the same therapy with the same regimen to allow evaluation of MIJ821 treatment response in the Extension Period.

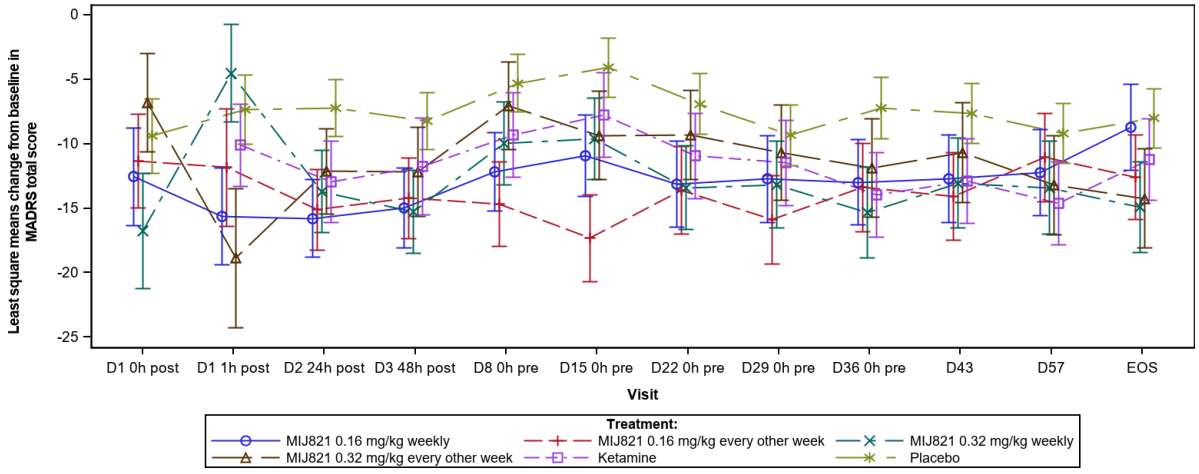
4.2 Rationale for dose/regimen and duration of treatment

Dose Selection

The four doses for this dose range finding study were selected based on the efficacy and safety data from the Phase 2a PoC study in treatment-resistant depression (CMIJ821X2201) and relevant health authority guideline for developing drugs for treatment of major depressive disorder.

Figure 4-1 shows the change in the MADRS score over the course of the trial based on the data of the PoC study CMIJ821X2201.

Figure 4-1 MMRM least-square means (SE) change from baseline in the total MADRS score. Intent-to-treat analysis set. Parameter: MADRS total Score.



Baseline is defined to be the last available measurement obtained before the first infusion on Day 1.

In the PoC study CMIJ821X2201, two doses were tested: 0.16 mg/kg and 0.32 mg/kg, and two different regimens for each dose (weekly and biweekly (every other week) administrations). The study was placebo controlled and included a ketamine treatment arm as a positive control.

The ANCOVA analysis of change from baseline in total MADRS score at 24 hours showed that there was a significant difference between both pooled MIJ821 groups and placebo, demonstrating superiority of MIJ821 treatment to placebo in reducing total MADRS score. The adjusted arithmetic mean difference was -8.25 ($p = 0.0013$) for the pooled MIJ821 0.16 mg/kg group versus the placebo group and -5.71 ($p = 0.0196$) for the pooled MIJ821 0.32 mg/kg group versus the placebo group (ketamine arm was -5.67 ($p=0.0461$). At 48 hours, the statistically significant decrease in the total MADRS score for both pooled MIJ821 groups versus placebo was maintained. At Week 6, there was a statistically significant ($p < 0.10$) decrease in the total

MADRS score for 2 of the 4 MIJ821 treatment groups versus the placebo treatment group. The MMRM analysis showed that the adjusted arithmetic mean difference was -5.42 (p = 0.0993) for the MIJ821 0.32 mg/kg weekly treatment group versus the placebo treatment group, and 6.46 (p = 0.0598) for the MIJ821 0.16 mg/kg biweekly treatment group versus the placebo treatment group (ketamine arm was - 5.24, p=0.0974). Although numerical differences were observed between other two treatment groups and the placebo treatment group, statistical significance was not reached (Figure 4-1). Given that the lower dose (0.16 mg/kg) was better tolerated than the higher dose (0.32 mg/kg), a biweekly dose of 0.16 mg/kg was therefore selected as the highest dose for this Phase 2b dose-range finding trial.

Once the highest dose to be tested was established, lower doses were selected in approximately 3-fold steps to minimize overlap of MIJ821 exposure between treatment groups. It is acknowledged that 0.016 mg/kg dose would be sufficiently low to achieve a 10-fold dose range, which is e.g. recommended by EMA (EMA 2015). However, based on a receptor occupancy (RO) study in rats, the RO in patients was predicted. For a dose of 0.016 mg/kg, the predicted peak RO is 78% (DMPKR2000343). This is not insignificant for a dose intended to be at the lower end of the dose-response profile. Therefore, the additional dose of 0.0048 mg/kg was included in this dose ranging trial. Based on modeling data at 0.004 mg/kg, the predicted peak of RO is 47%.

Dose Regimen

In the PoC study, in addition to the above mentioned results, MMRM analysis showed in the 0.16 mg/kg biweekly treatment arm, that the effect of MIJ821 over placebo on MADRS was maintained 2 weeks after the last drug administration (adjusted arithmetic mean difference -6.46, p = 0.0598; Day 43), and was diminished at 4 weeks after the last drug administration (adjusted arithmetic mean difference -1.86, p=0.3275; Day 57). In the 0.32 mg/kg biweekly treatment arm, the MMRM analysis showed that the effect of MIJ821 over placebo on MADRS was not as pronounced at both 2 and 4 weeks after the last drug administration respectively (adjusted arithmetic mean difference -3.06 , p =0.2491 at Day 43 and -4.00 p=0.1865 at Day 57). Because of this, two treatment arms with single dose administrations of MIJ821 and weekly MADRS measurements are included in this study to establish the duration of the MIJ821 effect. For the single dose administration regimen, the two highest doses of 0.16 mg/kg and 0.048 mg/kg were selected. It is of less interest to study single dose administrations for the lower doses (0.016 mg/kg, 0.0048 mg/kg) as the duration of their effect is expected to be shorter.

6 weeks treatment duration

According to FDA draft guidance for developing drugs for the treatment of major depressive disorder (FDA 2018), durability of effect beyond the initial response should be characterized.

Data from the proof of concept study (CMIJ821X2201) demonstrated that MIJ821 had a strong treatment effect compared to placebo for both 0.16 mg/kg and 0.32 mg/kg doses and this effect persisted at each assessment visit up to week 6 of study treatment.

Therefore, to demonstrate durability of effect beyond 24 hours (the primary endpoint), continued observation of drug-placebo differences over the 6-week double-blind Core Treatment Period was chosen.

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

Placebo as a comparator allows for the most objective assessment of the treatment effect, safety and tolerability of MIJ821. This is supported from a scientific point of view considering that MIJ821 will be a novel treatment for MDD patients who have suicidal ideation with intent. Use of placebo in Phase 2b trials in MDD is also justified and recommended by the regulatory guidelines, such as the draft FDA guidance for developing drugs for treatment major depressive disorder (FDA 2018) and EMA guideline for Clinical investigation of medicinal products in the treatment of depression (EMA 2013). Given that physicians would continue treating participants with pharmacological antidepressant, SoC treatment concomitantly with investigational drug, a placebo-controlled study is justified.

4.4 Purpose and timing of interim analyses/design adaptations

When all participants have completed double-blind Core Period and the 2 week Follow-up visit, an unblinded interim analysis will be performed to evaluate the dose-response relationship of MIJ821. The purpose of the unblinded interim analysis is to establish the optimal dose and dose regimen for further evaluation in Phase 3 studies. The optimal dose and dose regimen will be determined based on, but not limited to, primary efficacy and other efficacy endpoints, PK, and safety results obtained from the data that were generated and analyzed from the Core Period. See also Section 12.7 for more details.

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.

Non-Clinical Safety

The primary pharmacological properties of MIJ821 were characterized *in vitro* and *in vivo* and established a pharmacological basis for the intended clinical use. Nonclinical drug disposition and exposure effects were assessed. *In vivo*, MIJ821 was shown to distribute into the rat brain. The nonclinical safety profile of MIJ821 has been evaluated in rats and dogs using the intravenous (I V) route in safety pharmacology studies, in single dose neurotoxicity studies, and in repeated dose toxicity studies of up to 6 weeks of duration (twice weekly dosing). MIJ821 is not genotoxic and not phototoxic. In safety pharmacology, transient increases in heart rate were seen in dogs. MIJ821 affected the human ether-a-go-go-related (hERG) channel potassium current with an IC50 of 1.1 µM and a related free Cmax-based safety margin of 22-fold at the human dose of 0.16 mg/kg. MIJ821 did not induce neuronal vacuolation (“Olney lesions”) or neuronal necrosis. In pivotal studies, MIJ821 was tolerated with no adverse effects. The main targets identified included the central nervous system (CNS with clinical signs assumed to represent exaggerated pharmacological effects) and the cardiovascular system (with transient heart rate increases in dogs). No observed adverse effect levels (NOAELs) were identified in all pivotal studies with safety margins (at least 7-fold compared with human exposure at 0.32 mg/kg in terms of AUC) adequate for the pursued indication.

Clinical Safety

MIJ821 has been tested in a limited number of participants – in a FIH study (Phase 1 Study CMIJ821X2101) in healthy volunteers and a Phase 2a clinical study (CMIJ821X2201) in patients with TRD. Although it has been shown to be safe and well tolerated at the dosages to be used in this Phase 2b study, there may be unknown risks associated to MIJ821.

In the FIH study (CMIJ821X2101), dissociative and cognitive adverse events were dose-related, occurring at 0.24 mg/kg or higher doses, but not at 0.16 mg/kg or lower doses. Frequency of amnesia in particular was somewhat higher at 0.32 mg/kg than other doses. With repeated dosing, dissociative and cognitive adverse events were seen only in two participants in the 0.32 mg/kg group. Dissociative and cognitive adverse events were mild, had time to onset after infusion of 0.78-4.43 hours, and resolved in 0.67-5.4 hours. Amnesia had a longer time to onset (range of onset 0.83-7.93 hours) and lasted longer (range to resolution 0.02-23.85 hours). Other adverse events were not common, nor severe.

In the PoC Study CMIJ821X2201 conducted in 70 treatment-resistant depression patients for 6 weeks, the clinical picture with longer observation on treatment was consistent with FIH data. The study also included one Ketamine treatment arm as a positive control.

Most AEs were mild in severity and were reported in 39 subjects (55.7%). Moderate and severe AEs were reported in 13 (18.6%) and 10 (14.3%) subjects, respectively and one life-threatening AE of suicide threat was also reported in one subject (MIJ821 0.32 mg/kg biweekly treatment group). SAEs occurred in 5 subjects: in the MIJ821 0.16 mg/kg biweekly treatment group, 1 subject had an asthma exacerbation; in the MIJ821 0.32 mg/kg biweekly treatment group: 3 subjects experienced 4 SAEs: one subject with atrial fibrillation, one subject with worsening of major depression, and in one subject two SAEs: suicide threat (Day 29) and suicide attempt (Day 70). In the placebo treatment group one subject had a suicide attempt. All SAEs were assessed as not study drug related by the investigator.

Analysis of AEs of interest showed that dissociative side effects, sedation and amnesia (investigator reported) were seen at both the 0.16 mg/kg and 0.32 mg/kg MIJ821 doses. Amnesia in particular was dose dependent and more common at the higher MIJ821 dose (42.1% with MIJ821 0.32 mg/kg vs 9.5% with MIJ821 0.16 mg/kg pooled doses). No AEs of amnesia was seen in Ketamine or Placebo arms. About one-quarter of patients in each active treatment group experienced dissociative side effects (23.8% for 0.16 mg/kg pooled dose and 26.3% in 0.32 pooled mg/kg dose), versus 50% with Ketamine and 10% with placebo. Sedation was seen at both active doses (14.3% at the lower pooled dose and 21.1% at 0.32 mg/kg pooled dose vs 10% with ketamine and 0% with placebo).

Time to onset of dissociative side effects, amnesia and sedation was short, occurring within the 40 minutes of infusion in most cases for both MIJ821 doses and for placebo, though somewhat longer than with ketamine. Median time to onset for adverse event of sedation was shorter for the lower MIJ821 dose (pooled 0.16 mg/kg dose, 0.25 hours) than the higher dose (pooled 0.32 mg/kg dose, 1.46 hours), versus 0.10 hours for ketamine and no cases (0.0 hours) for placebo.

Most events of amnesia resolved within 4 hours (median time to resolution was 3.27 hours). Median time to resolution for dissociation ranged from 5.25 hours for MIJ821 0.16 mg/kg

pooled dose versus 3.72 hours for MIJ821 0.32 mg/kg pooled dose, and shorter times for ketamine (1.02 hours) and placebo (2 hours). Events of sedation resolved faster for the pooled 0.16 mg/kg dose than 0.32 mg/kg pooled dose (median time 1.6 hours vs 2.5 hours). Ketamine time to resolution was 0.47 hours.

At both MIJ821 investigated doses, increases in mean supine systolic and diastolic blood pressure were observed at the first sampling time of 1 hour after start of the 40 min infusion. The placebo-adjusted mean change from baseline in supine SBP and DBP appeared to peak between 2 to 4 hours after start of infusion (< 20 mmHg) with a clear trend of recovery to baseline within 4 hours (DBP) and 6 hours (SBP) after start of infusion.

Efficacy

The Phase 2 proof of concept study in TRD patients (CMIJ821X2201) evaluated two different active MIJ821 doses of 0.16 mg/kg and 0.32 mg/kg given in two different regimens - weekly and biweekly (every other week). Based upon the final data of this study, patients on MIJ821 reported significant improvement on MADRS score at 24 h and at 6-weeks timepoint upon repeated treatment. The results show that MIJ821 was effective at all time points, especially in the lowest dose (i.e. 0.16 mg/kg every week or every other week; MADRS improvement over placebo at 24 h was 8.25 points, p = 0.0013; 0.32 mg/kg every week or every other week; MADRS improvement over placebo at 24 h was 5.71 points, p = 0.0196). Similarly, in the ketamine group MADRS improvement over placebo at 24 h was 5.67 points, p = 0.0461. At 48 hours, the statistically significant decrease in the total MADRS score for both pooled MIJ821 groups and for Ketamine versus placebo was maintained. At Week 6, there was a statistically significant ($p < 0.10$) decrease in the total MADRS score for 2 of the 4 MIJ821 treatment groups versus the placebo treatment group. The MMRM analysis showed that the adjusted arithmetic mean difference was -5.42 (p = 0.0993) for the MIJ821 0.32 mg/kg weekly treatment group versus the placebo treatment group, and -6.46 (p = 0.0598) for the MIJ821 0.16 mg/kg biweekly treatment group versus the placebo treatment group and -5.24 (p = 0.0974) for the Ketamine group versus the placebo treatment group.

Overall, the totality of the safety data suggests that MIJ821 is generally safe and well tolerated, and has a positive risk-benefit ratio.

Summary of risks

The risks of participating in the study include those identified in the clinical studies with MIJ821 mentioned above, those associated with IV infusion and those associated with blood sampling. The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, treatment interruptions or discontinuation rules, as well as close clinical monitoring, including hospitalization during Screening and within the recommended observation period of 72 hours after the first intravenous infusion of study drug (with shorter or longer hospitalization duration allowed if clinically warranted per local standard practice, but not less than 24 hours) and hospital discharge criteria. In addition, the Data Monitoring Committee (DMC) will conduct ongoing safety reviews (refer to Section 10.2.6).

Based on the totality of the available patient safety data, a 4-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 observational 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 time point 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.

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.

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

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

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 highly effective methods for contraception as outlined in the exclusion criteria Section 5.2 and Section 8.4.4. If there is any question that the participant will not reliably comply, he/she should not be entered or continue in the study.

Based on currently available information, considering the ketamine safety profile and clinical/non-clinical evidence available for MIJ821, the following events are considered Adverse Events of Special Interest (AESI). This information is subject to change, based on the

availability of incremental clinical experience with MIJ821. Please refer to the current MIJ821 IB 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 other lower urinary tract adverse events

The list of current adverse events of special interest is available in the IB. Also refer to Section 10.2.5.

Expected benefits

Participants randomized to MIJ821 may benefit from receiving a potentially effective pharmacological treatment for MDD, in addition to the SoC they would normally be receiving.

5 Study Population

The study population will consist of male and female participants ≥ 18 years old to ≤ 65 years old with MDD who have suicidal ideation with intent. The goal is to randomize a total of approximately 195 participants in approximately 50-70 centers worldwide. Randomized patients that prematurely discontinue will not be replaced.

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), body weight from 50 kg to 120 kg (inclusive) at screening
3. DSM-5 defined major depressive disorder (MDD) with a current major depressive episode (MDE) without psychotic features at the time of screening based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.), Module A (Major Depressive Episode) assessed at Screening
4. Participants must have current suicidal ideation with intent, confirmed by a "Yes" response to Question B3 AND either Question B10 or Question B11 obtained from the M.I.N.I. Suicidality, Module B (Suicidality) assessed at Screening
5. Current suicidal ideation with intent, confirmed by "Yes" (>0) response to Question 3 AND either Question 9 or Question 10 obtained from the S-STS at Baseline
6. Montgomery-Åsberg Depression Rating Scale (MADRS) score > 28 at Screening and before randomization on Day 1
7. Participants 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 local treatment guidelines) during the trial duration

8. In the physician's opinion, acute psychiatric hospitalization is clinically warranted to treat the patient's condition, and the patient is either already in the hospital or agrees to be hospitalized voluntarily for the required per protocol period (duration is defined in Section 3)

5.2 Exclusion criteria

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

1. Any prior or current diagnosis of bipolar disorder, MDD with psychotic features, schizophrenia, or schizoaffective disorder as obtained from M.I.N.I., Module C (Manic and Hypomanic Episodes) and Module K (Psychotic Disorders and Mood Disorders with Psychotic Features) assessed at Screening
2. Patients with acute alcohol or substance use disorder or withdrawal symptoms requiring detoxification, or patients who went through detoxification treatment (inpatient or outpatient) within 1 month before Screening. M.I.N.I. Module I (Alcohol Use Disorder) and Module J (Substance Use Disorder, Non-Alcohol) should be conducted at Screening
3. Participant has a current clinical diagnosis of autism, dementia, or intellectual disability
4. History of seizures. Note: childhood febrile seizures are not exclusionary
5. Participants with current borderline personality disorder as obtained from M.I.N.I., Module Y (Borderline Personality Disorder) assessed at Screening.
6. Participants with suicidal ideation or behavior caused primarily by another non-MDD condition, as obtained from M.I.N.I., Module Z (Suicidality Disorders Classification Interview) assessed at Screening
7. Known worsening or new appearance of suicidal ideation or behavior during a prior treatment with ketamine or esketamine or within 2 months after last ketamine or esketamine administration
8. Active hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) or active COVID infection as per medical history and/or available medical records
9. History of hypersensitivity to the study drugs or its excipients or to drugs of similar chemical classes.
10. Participants taking medications prohibited by the protocol (see Section 6.2.2, Table 6-2)
11. Intake of the following medications :
    a. Esketamine or Ketamine within 2 months before Screening
    b. Monoamine oxidase inhibitors (MAOIs) within 14 days before Screening
12. Cardiac or cardiac repolarization abnormality, including any of the following:
    a. History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
    b. History of clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade 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 pre first dose on Day 1, or inability to determine the QTcF interval

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:
    a. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
    b. Concomitant medication(s) with a "Known Risk of Torsades de Pointes" that cannot be discontinued or replaced by safe alternative medication 7 days prior to Screening and during the Core.
15. Participant has mean systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg at Screening and pre first dose on Day 1; or any past history of hypertensive crisis, or participants in which the elevation of blood pressure or intracranial pressure poses a serious risk e.g. subjects with aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels); subjects with history of intracerebral haemorrhage
16. 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, impede compliance or hinder completion of the study.
17. Have evidence of significant renal insufficiency, indicated by an estimated glomerular filtration rate (eGFR) of < 40 mL/min/1.73 m^2 at Screening
18. Use of other investigational drugs within 30 days of Screening
19. Pregnant or nursing (lactating) women
20. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 1 week after stopping study treatment (in the Core and Extension in case of retreatment). 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. In addition, male participants must not donate sperm for the period specified above.
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 1 week after stopping medication (applies to the Core and Extension at the time of retreatment).

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). 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).

Oral contraception or systemic hormonal contraception (e.g. transdermal or implanted hormonal methods) is not allowed for the purpose of contraception.

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.

Patients eligible to receive MIJ821 treatment for relapse in the Extension Period should not be pregnant prior to the start of the treatment (see also Section 8.4.4 for additional details).

6 Treatment

6.1 Study treatment

Study treatment consists of MIJ821 or placebo in combination with pharmacological SoC.

MIJ821 20 mg will be centrally supplied as lyophilized powder in vials (pharmaceutical form). This will be reconstituted with 0.9% sodium chloride to obtain the solution for infusion for all MIJ821 doses. Placebo will consist of 0.9% sodium chloride infusion bag supplied by the site.

The first infusion of study treatment (Day 1) must be administered while the participant is hospitalized. All subsequent administrations may be performed either under hospitalization or as an outpatient in the clinic, at investigator's discretion.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

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

The investigational treatment for this study will be MIJ821. Due to the difference in preparation between MIJ821 and placebo and the requirement for the intravenous MIJ821 dose to be prepared on a mg/kg basis for intravenous infusion for the active treatment arms, an unblinded qualified site personnel, independent of the investigational staff, is required to maintain the blind. Please refer to Section 6.4 for additional details.

6.1.2 Additional study treatments

No other pharmacological treatment beyond investigational drug, control drug (placebo) and antidepressant pharmacological SoC are included in this study. Patients are also allowed psychotherapy.

6.1.3 Treatment arms/group

This study consists of seven treatment arms, participants will be randomized in a 2:1:2:2:2:2:2 ratio on Day 1 to the following treatment arms on the top of the ongoing SoC:

- Placebo, one infusion every other week on Day 1, Day 15 and Day 29 of treatment (Core Period only)
- MIJ821 fixed dose of 0.0048 mg/kg, one infusion every other week on Day 1, Day 15 and Day 29 of treatment/ relapse retreatment
- MIJ821 fixed dose of 0.016 mg/kg, one infusion every other week on Day 1, Day 15 and Day 29 of treatment/ relapse retreatment
- MIJ821 fixed dose of 0.048 mg/kg, one infusion every other week on Day 1, Day 15 and Day 29 of treatment/ relapse retreatment
- MIJ821 fixed dose of 0.16 mg/kg, one infusion every other week on Day 1, Day 15 and Day 29 of treatment/ relapse retreatment
- Single administration MIJ821 0.048 mg/kg, one infusion on Day 1, followed by placebo infusions every other week on Day 15 and Day 29 of treatment / relapse retreatment
- Single administration MIJ821 0.16 mg/kg, one infusion on Day 1, followed by Placebo infusions every other week on Day 15 and Day 29 of treatment / relapse retreatment

In all treatment arms, investigational treatment will be administered by intravenous infusion every other week, 3 infusions in total during the placebo-controlled double-blind Core, 6-week period of the study.

6.1.4 Treatment duration

One course of treatment in the core and extension period is defined as 3 infusions administered bi-weekly (Day 1; Day 15; Day 29).

Core Period

All participants who are randomized in the double-blind Core Period will receive three doses of investigational treatment or placebo once every 2 weeks over a total period of 6 weeks.

Extension Period

If relapse criteria are met during the Extension Period, participants will be treated with the same blinded dose and regimen they received during the Core period, receiving three i.v. infusions of investigational treatment once every 2 weeks, for a total period of 6 weeks. Participants receiving placebo in the Core Period, will be randomized in a blinded manner at the time of the initial randomization to one of the active treatment arms to receive treatment for relapse in the Extension Period in case they meet the required criteria at the End of Core (see Section 3.4 for more details).

Only one course of three i.v. infusions of investigational treatment once every 2 weeks will take place in the extension. No second course of retreatment will be allowed. In case of clinical worsening after retreatment for relapse, the patient would not receive further retreatment with

the study drug. Patient will be managed as per see Section 3.3 subsection Follow up duration and Section 3.4 subsection Relapse and Clinical Worsening.

Once the dose and dose regimen for Phase 3 have been selected following completion of the interim analysis, participants experiencing a relapse who have not yet started retreatment will receive the selected Phase 3 dose and regimen in a dose-blinded manner. Patients who have already started treatment for the relapse will continue on the originally assigned dose.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All participants must receive pharmacological antidepressant therapy during the Core Treatment Period and 52 weeks Extension Period. Pharmacological treatment may include an antidepressant, or antidepressant plus augmentation therapy (e.g. antipsychotics, lithium, etc). Dosage titration or adjustments of standard-of-care antidepressant treatment occurring during the first 2 weeks of double-blind treatment are allowed, if needed, with dosages maintained thereafter during the Core period.

Psychotherapy will also be allowed and any change must be appropriately documented in the source records and CRF.

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

During the Extension Period, pharmacological antidepressant therapy can be modified only for non responders or participants who did not achieve remission (see Section 3.2 for more details).

Those participants, who are classified as a responder or remitter at the End of the Core Period must maintain a stable SoC (see Section 3.2 for more details). In case of a relapse, the SoC pharmacological treatment can be adjusted, if needed, during the first 2 weeks of retreatment. Participants may or may not be hospitalized for the treatment of relapse (as per clinical judgment and local practices).

Participants who are responder or remitter at the End of the Core Period, and relapse during the Extension Period but do not meet the weight requirements of 50-120kg (inclusive) to be retreated in case of relapse, may change their SoC, as required, and should discontinue the Extension as defined in Section 3.3 Follow-up Duration.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms (CRFs).

Potential interactions

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 (fluoxetine, paroxetine and bupropion) on the exposure of MIJ821 has been investigated in drug-drug interaction (DDI) simulations by means of the SimCYP® software. The simulated Cmax values were ≤ 1.3-fold higher in the presence of fluoxetine or paroxetine and the AUC values ≤ 2-fold for all CYP2D6 genotypes (poor, extensive, or ultra-metabolizers). At doses ≤ 0.16 mg/kg, the resulting mean exposure in the presence of strong CYP2D6 inhibitors are within the exposure range investigated in the FiH study (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.
- Furthermore, in the PoC study (CMIJ821X2201, doses: 0.16 and 0.32 mg/kg), approximately 70% of patients 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 experiences (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 adverse events due to an exposure increase by CYP2D6 inhibition is considered to be low for the proposed MIJ821 doses being less or equal to 0.16 mg/kg. In conclusion, CYP2D6 inhibitors are allowed as co-medications. Nevertheless, caution has to be taken when strong CYP2D6 inhibitors are administered (see Section 6.2.1.1). All concomitant medications will be recorded.

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 the SimCYP® software. No exposure increase of both probe substrates has been estimated at the highest tested MIJ821 dose of 0.48 mg/kg. 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 MIJ821 doses ≤ 0.16 mg/kg.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The investigator should instruct the participant to notify the study site about any new medications he/she takes after the participant is randomized in the study. All medications, procedures and significant non-drug therapies administered after the participant is enrolled into the study must be recorded.

The following medications should be administered with caution due to safety reasons and/or potential confounding factor for safety assessments.

- Antihypertensive medications should preferably be taken in the morning before dosing.
- Any benzodiazepines (including alprazolam and midazolam) are permitted at dosages up to the equivalent of 6 mg/day of lorazepam, for episodic or chronic use (see below for Benzodiazepines with their corresponding maximum dosages). They should not be should not be taken within 12 hours of each study visit and for/within 4 hours after dosing (see Table 6-2), unless given as a rescue medication - see Section 6.2.3 for more details
- Cough decongestants are allowed, but should not be taken within 12 hours of each study visit and for/within 4 hours after dosing.

- Benztropine and diphenhydramine can only be used on a PRN basis and not within 12 hours of each study visit.
- Participants must not use alcohol, cannabis or psychostimulants (amphetamines, methylphenidate, modafanil, armodafinil etc.) within 24 hours before each study visit and 24 hours after end of infusion. If the use is identified by a urine test and confirmed by the assessment of the investigator or delegate at the visit (see Section 8.4.1 for details), or if a participant appears intoxicated, the visit should be delayed as per the permitted visit window see Section 8 for more details.
- Opioids must not be used within 24 hours before each study visit and 24 hours after end of infusion.
- Inhaled, intranasal, topical, and ophthalmic steroids are allowed. Intermittent oral, i.m./i.v. corticosteroids are permitted (chronic use prohibited).
- Trazodone must not be used within 24 hours before each study visit and 24 hours after end of infusion.
- For patients taking strong CYP2D6 inhibitors (berberine, bupropion, dacomitinib, fluoxetine, paroxetine, quinidine), the infusion period should be monitored with extra caution. All safety observations occurred during or after the end of infusion should be carefully observed for increased or unexpected frequency and severity. Infusion interruptions (i.v. infusion lasts less than 40 minutes), treatment interruptions (when subsequent i.v. dosing(s) is not performed) or study treatment discontinuation may apply in case of a safety concern, as defined in Sections 6.6.2, Section 9.1.1, Section 10.2, and Section 16.

Examples of Benzodiazepines with their corresponding maximum dosages:

- Lorazepam administered i.m. or p.o. (maximum daily dose 6 mg)
- Midazolam administered i.m. or p.o. (maximum daily doses 0.2 to 0.25 mg/kg not to exceed 20 mg)
- Clonazepam administered p.o. (maximum daily dose 4 mg)
- Alprazolam administered p.o. (maximum daily dose 4 mg in divided doses)

In case of a prohibited use, visit reschedule should be considered as per the permitted visit window - see Section 8 for more details.

Each medication should be evaluated for the potential additive effect(s) of sedation, dissociation, suicidality, cardiovascular and respiratory effects, impact on memory and cognitive functions. Medications with a potential impact should be avoided for at least one half-life before each study visit and one half-life after each study drug administration.

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 all-inclusive. Each medication should be evaluated for the 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 medication

Medication	Prohibition period	Action taken to study treatment***	Reason
Ketamine Esketamine	2 months before Screening and during the whole study duration (Core and Extension)	Discontinue study treatment if in the Core or discontinue study if in the Extension	Safety and PD interaction -additive effects (NMDA receptor antagonists)
Electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), Deep brain stimulation (DBS), and Vagus nerve stimulation (VNS)	After Screening and during the whole study duration (Core and Extension)	Discontinue study treatment if in the Core or discontinue the study if in the Extension	PD interaction
Amantadine	After Screening and during the whole study duration (Core and Extension)	Discontinue study treatment if in the Core or Discontinue the study if in the Extension	Safety (CNS additive effects) and PD interaction (weak non-competitive NMDA receptor antagonist)
Monoamine oxidase inhibitors (MAOIs)	14 days before Screening, during the Core, and during the time of relapse retreatment (including 14 days before retreatment)	None	Safety (additive risk of hypertension effect and potential for precipitating hypertensive crisis) and PD interaction
Citalopram and Escitalopram	After Screening, during Core, and during the time of relapse retreatment + 1 week after last MIJ821 dosing	None	Safety (additive risk of QT prolongation, known risk of Torsades de Pointes)
Medications with a “Known Risk of Torsades de Pointes” per www.qtdrugs.org and Table 16-7	7 days before Screening, during Core, and during the time of relapse retreatment + 1 week after last MIJ821 dosing	None	Safety (additive risk of QT prolongation, risk of Torsades de Pointes)
Amitryptyline, Nortryptyline	Within 24 hours prior to each study visit**and up to at least 4 h after end of infusion	None	Safety (additive risk of QT prolongation, risk of Torsades de Pointes)
Quetiapine	Within 12 hours prior to each study visit**and up to at least 4 h after end of infusion	None	Safety (additive risk of QT prolongation, risk of Torsades de Pointes)
Oral and Systemic Hormonal Contraceptives for contraception purposes	After Screening, during Core, and during the time of relapse retreatment+ 1 week after last MIJ821 dosing	None	Not accepted as highly effective contraception method until a dedicated clinical study shows no drug-drug interaction between MIJ821 and hormonal contraceptives
Systemic Corticosteroids	Chronic use is prohibited after Screening, during Core, and during the time of relapse retreatment	None	Safety (additive cardiovascular and neuropsychiatric effects)
Benzodiazepines (including alprazolam and	Within 12 hours prior to each study visit** and up	None*	Safety (additive sedative effect) and confounding

Medication	Prohibition period	Action taken to study treatment***	Reason
midazolam) at dose equivalent of up to 6 mg/d Lorazepam	to at least 4 h after end of infusion, unless given as a rescue medication to treat agitation , anxiety or aggressive behavior		effect for safety assessments
Cough decongestants	Within 12 hours prior to each study visit**and up to at least 4 h after end of infusion	None*	Safety (additive sedative effects) and confounding effect for safety assessments
Benztropine and diphenhydramine	Within 12 hours prior to each study visit**. Continuous use is prohibited	None*	Safety (additive sedative effect) and confounding effect for safety assessments
Trazadone	Within 24 hours prior to and 24 hours after each study drug infusion	None*	Safety (additive Risk of QT prolongation)
Alcohol	Within 24 hours prior to each study visit and 24 hours after end of infusion	None*	Safety (additive sedative and CNS effects), confounding effect for safety and efficacy assessments
Cannabis and Psychostimulants (amphetamines, methylphenidate, andmodafanil, armodafinil etc.)	Within 24 hours prior to each study visit and 24 hours after end of infusion	None*	Safety (additive CNS effects), confounding effect for safety and efficacy assessments
Opioids	Within 24 hours prior to each study visit and 24 hours after end of infusion	None*	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 - see Section 8.4.1 for more details

** With the exception of the screening visit

*** Participants who are in the two-month follow-up period should continue the follow-up even in case 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 source documents and the CRFs:

For agitation, anxiety or aggressive behaviour (per investigator judgement 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).

For acute suicidality (e.g. self harm), please refer to Section 3.2 hospitalization, and Section 10.2.5 adverse events of special interest

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

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant will be identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained throughout his/her participation in the study. 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 (ICF), 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.

6.3.2 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 unblinded site personnel will contact the IRT after confirming 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 patient 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.

The randomization scheme will include the treatment assignment in both the Core period and Extension period. Participants who are randomized to one of the active MIJ821 arms in the Core Period, will be assigned to the same blinded dose and dosing regimen (i.e. 3 i.v. infusion of MIJ821 or 1 i.v. infusion of MIJ821 followed by 2 i.v. infusions of placebo) of MIJ821 in the Extension Period. Participants who are randomized to the placebo arm in Core Period, will be assigned to one of the MIJ821 treatment arms (equally to MIJ821 dose groups except for 0.0048 mg/kg every other week with only half proportion) in Extension Period.

The switch to optimal dose/dose regimen post interim analysis is defined in Sections 3.3 and Section 6.1.4.

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

6.4 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; and the clinical trial team (CTT) from the time of randomization until interim analysis; 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 an unblinded qualified site personnel.

To minimize the risk of introducing bias, different site personnel must perform efficacy and safety assessments as described in Section 8.3.

At the time of interim analysis, the Novartis global clinical team will be unblinded. However, participants, investigators, site personnel, persons performing the assessments, will remain blinded to the results of the interim analysis and the identity of the treatment until final database lock.

Open label supply of MIJ821 will be provided at sites to the unblinded site personnel.

The randomization codes associated with participants from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until the interim analysis.

Unblinding will occur in the case of participant emergencies, at the time of interim analysis (for the CTT only), and at the conclusion of the study. The DMC will conduct ongoing unblinded safety reviews (see Section 10.2.6).

6.5 Dose escalation and dose modification

Investigational drug dose adjustments are not permitted. Infusion interruptions (i.v. infusion lasts less than 40 minutes) or treatment interruptions (when subsequent i.v. dosing(s) is not performed) are allowed as described in Section 6.6.2, Section 10.2, and Section 16.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

During both the double-blind Core Treatment Period and the Extension Treatment Period for relapse, the study medication will be administered by the investigator or designated study staff at each visit. The time of administration information should be captured in the source documents and the CRF at each visit during which the intravenous infusion is administered. All study treatment administered, including study drug infusion interruptions, must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

Each adverse event should be carefully evaluated by the investigator and treatment should be considered individually based on the clinical judgement of the investigator and local treatment

practices. Medication used to treat adverse events (AEs) must be recorded on the appropriate CRFs.

Each medication should be evaluated for the potential additive effect(s) of sedation, dissociation, suicidality, cardiovascular and respiratory effects, impact on memory and cognitive functions. Medications with a potential impact should be avoided for at least their one half-life before each study visit and one half-life after each study drug administration.

For agitation or anxiety midazolam (maximum dose 2.5 mg orally or i.m.) or short acting benzodiazepine may be used (see also Section 6.2.3).

For cardiovascular effects, specifically for blood pressure increase, unless clinically indicated, it is recommended that transient increases in blood pressure not be treated unless clinically indicated, 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.

In case of a study drug infusion interruption due to a safety reason (e.g. a (serious) adverse event appears during the study drug infusion and requires an urgent medical treatment or intervention), the investigator should also consider the appropriateness of the next study drug administration(s) based on careful evaluation of the risk-benefit ratio for this particular patient. Study drug treatment interruption in the Cor and in the Extension or treatment discontinuation may be considered, where necessary and appropriate. Please also refer to Section 4.5, Section 9, Section 10.2, and Section 16 for further details.

6.6.3 Emergency breaking of assigned treatment code

Emergency code break must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation 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 the investigator is unavailable, to ensure that un-blinding can be performed at any time.

6.7 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 (MIJ821 or placebo) to be dispensed by contacting the IRT. The medication number(s) for the investigational treatment (MIJ821) will be obtained via IRT. The investigational treatment has a 2-part label (base plus tear-off label). A unique medication number is printed on the label. Immediately before dispensing the investigational treatment kit, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Placebo will be sourced locally. For details on preparation, refer to the pharmacy manual.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

Clinical supplies are to be used 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 visits or remotely and 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 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.

6.7.2 Instruction for prescribing and taking study treatment

Administration of the intravenous infusion of the study treatment should be monitored in an inpatient setting for the first dose on Day 1 and inpatient or outpatient during the study. The

infusion takes 40 minutes to administer. An observation period of a minimum of 4 hours will follow each dose administration.

Participants will be administered the intravenous infusion of the study treatment in the clinic or facility at approximately the same time, in the morning or early afternoon at the latest.

On days that PK samples are obtained, the participant will be administered the study treatment during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples. It has to be emphasized that the infusion site must be from the contralateral arm (i.e., opposite arm) of the PK sampling site.

On Day 1, no food is allowed from 4 h pre-dose to 1hr after infusion start and the time of food intake prior and following the first intravenous infusion should be recorded in the CRF.

The dose calculation is based on the treatment arm and the participant's body weight. If a participant experiences a relapse during the extension period but is no longer meeting the weight range of 50-120 kg (inclusive) due to prior weight gain or loss, the participant cannot be retreated in case of relapses (see Section 3.3 for further details).

Table 6-3 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
MIJ821 20 mg	0.0048 mg/kg	Days 1, 15, 29 Given in the Core and for relapse treatment in Extension
MIJ821 20 mg	0.016 mg/kg	Days 1, 15, 29 Given in the Core and for relapse treatment in Extension
MIJ821 20 mg	0.048 mg/kg	Days 1, 15, 29 Given in the Core and for relapse treatment in Extension
MIJ821 20 mg	0.16 mg/kg	Days 1, 15, 29 Given in the Core and for relapse treatment in Extension
MIJ821 20 mg and Placebo	0.048 mg/kg and 0.9% sodium chloride solution	MIJ821 dose on day 1, placebo on days 15 and 29 Given in the Core and for relapse treatment in Extension
MIJ821 20 mg and Placebo	0.16 mg/kg and 0.9% sodium chloride solution	MIJ821 dose on day 1, placebo on days 15 and 29 Given in the Core and for relapse treatment in Extension
Placebo	0.9% sodium chloride solution	Days 1, 15, 29 Given in the Core period only

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 under the Section 6.1.1 (Investigational and control drugs).

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 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the 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, Pregnancy Outcomes Reporting Consent for female subjects or the female partners of any male subjects who took study treatment
- As applicable, the female partner of male participants consents to the use of highly effective methods of contraception.

[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.

[redacted]

Declining to participate in these optional assessments will in no way affect the participant’s ability to participate in the main research study.

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

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments as well as when they are performed. All data obtained from these assessments must be supported in the participant's source documentation and recorded in the clinical database, received electronically or in source only, as indicated.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible (± 3 days visit window is allowed). Missed or rescheduled visits should not lead to automatic discontinuation.

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, patients may have unscheduled visits at the discretion of the Investigator. Data collected during unscheduled visits will be recorded in the unscheduled visit CRFs. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all adverse events and concomitant medications should be recorded on the CRFs.

Please see Appendix 6 for the scales recall periods.

If the 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.

Table 8-1 Assessment Schedule, Core and Extension

Period	**Screening**	**Core Period**																		
Visit Name	**Screening**	**Day 1 (1st infusion)**							**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**		
Days	**-2 to -1**	**1**							**2**	**8**	**15**						**22**	**29**		
Time (post-dose)	**-**	**-2h ±1[2]**	**-1h**	**0h**	**20min**	**40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**
Informed consent	X																			
Demography	X																			
Medical history/current medical conditions	X																			
Mini International Neuropsychiatric Interview (MINI)	S																			
Inclusion / Exclusion criteria	X	X																		
Physical Examination	S																			
Short Physical Examination		S									S							S		
25h Holter monitoring		X[3]	X																	
Electrocardiogram (ECG)[4]	X	X			X	X		X	X			X		X		X			X	
Pulse rate[4]	X	X			X	X	X	X	X	X		X		X	X	X	X		X	
Blood Pressure[4]	X	X			X	X	X	X	X	X		X		X	X	X	X		X	
Respiratory Rate	S	S			S	S	S	S	S	S		S		S	S	S	S		S	
Body Temperature	X											X							X	
Body Weight	X											X							X	

Period	**Screening**	**Core Period**																		
Visit Name	**Screening**	**Day 1 (1st infusion)**							**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**		
Days	**-2 to -1**	**1**							**2**	**8**	**15**						**22**	**29**		
Time (post-dose)	**-**	**-2h ±1[2]**	**-1h**	**0h**	**20min**	**40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**
Body Height	X																			
Pregnancy and assessments of fertility	X[5,7]		S[6]								S[6]							S[6]		
Hematology	X[7]								X	X	X						X	X		
Urinalysis	X[7]								X	X	X						X	X		
Clinical Chemistry	X[7,8,9]								X	X	X						X	X		
Alcohol Test and Drug Screen [10]	S									S	S						S	S		
Memory Assessment Questions						S[1]								S[1]						
Oxygen saturation		S[11]									S[11]							S[11]		
PK blood collection			X		X	X		X	X			X		X		X			X	
[redacted]																				
Montgomery-Asberg Depression Rating Scale (MADRS)	X	X						X	X	X	X					X	X	X		
Sheehan - Suicidality Tracking		X	[redacted]																	

Period	**Screening**	**Core Period**																	
Visit Name	**Screening**	**Day 1 (1st infusion)**							**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**		
Days	**-2 to -1**	**1**							**2**	**8**	**15**						**22**	**29**		
Time (post-dose)	**-**	**-2h ±1[2]**	**-1h**	**0h**	**20min**	**40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**
[redacted]																				

Period	**Screening**	**Core Period**																		
Visit Name	**Screening**	**Day 1 (1st infusion)**							**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**		
Days	**-2 to -1**	**1**							**2**	**8**	**15**						**22**	**29**		
Time (post-dose)	**-**	**-2h ±1[2]**	**-1h**	**0h**	**20min**	**40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**
[redacted]																				
Study drug administration				X[14,15]									X[15]							X[15]
Concomitant medications	X	X																		
[redacted]																				
Adverse Events		X[16]																		
Study completion information																				

Period	**Core Period**					**Extension**			**End of Study**
Visit Name	**Day 29 (3rd infusion)**			**Day 36**	**End of Core**	**2 weeks F/U[17]**	**4 weeks F/U[17]**	**Every 4 weeks[18]**	**End of Study**
Days	**29**			**36**	**43**	**57**	**71**	**99**	**-**
Time (post-dose)	**40min**	**2h**	**4h**	**-**	**-**	**-**	**-**	**-**	**-**
Informed consent									
Demography									
Medical history/current medical conditions						X			
Mini International Neuropsychiatric Interview (MINI)									
Inclusion / Exclusion criteria									
Physical Examination									
Short Physical Examination					S	S	S	S	S
25h Holter monitoring									
Electrocardiogram (ECG)[4]	X		X		X				X
Pulse rate[4]	X	X	X	X	X	X	X	X	X
Blood Pressure[4]	X	X	X	X	X	X	X	X	X
Respiratory rate	S	S	S	S	S	S	S	S	S
Body Temperature					X	X	X	X	X
Body Weight					X	X	X	X	X
Body Height									
Pregnancy and assessments of fertility					S[5]				S[5]
Hematology				X	X	X			X
Urinalysis				X	X	X			X
Clinical Chemistry				X	X[8]	X			X
Alcohol Test and Drug Screen [10]				S	S	S	S	S	S
Memory Assessment Questions	S[1]								
Oxygen saturation	S[11]								

Period	**Core Period**					**Extension**			**End of Study**
Visit Name	**Day 29 (3rd infusion)**			**Day 36**	**End of Core**	**2 weeks F/U[17]**	**4 weeks F/U[17]**	**Every 4 weeks[18]**	**End of Study**
Days	**29**			**36**	**43**	**57**	**71**	**99**	**-**
Time (post-dose)	**40min**	**2h**	**4h**	**-**	**-**	**-**	**-**	**-**	**-**
PK blood collection	X		X						
[redacted]									
Montgomery-Asberg Depression Rating Scale (MADRS)			X	X	X	X	X	X	X
[redacted]									

Period	**Core Period**					**Extension**			**End of Study**
Visit Name	**Day 29 (3rd infusion)**			**Day 36**	**End of Core**	**2 weeks F/U[17]**	**4 weeks F/U[17]**	**Every 4 weeks[18]**	**End of Study**
Days	**29**			**36**	**43**	**57**	**71**	**99**	**-**
Time (post-dose)	**40min**	**2h**	**4h**	**-**	**-**	**-**	**-**	**-**	**-**
[redacted]									
Study drug administration									
Concomitant medications	X								
[redacted]									
Study completion information									X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Subsequently, if memory gaps/ amnesia is present, it must be assessed at least once per hour until resolution
[2] Baseline assessments
[3] Equip participant with Holter monitoring device to be able to start the recording at -1 H predose.
[4] Triplicate
[5] Serum, (FSH test to be performed locally for fertility assessment, see Section 8.4.4)
[6] Urine
[7] If a result has not been obtained by a central lab, local lab result will be used to determine patient eligibility.
[8] In addition for this visit TSH test
[9] In case sample is not taken in fasting stage, a repeat chemistry sample must be done on day 1, in fasting condition.
[10] Results to be obtained before collection of any clinical and patient questionnaires
[11] Every 15 minutes from pre-dose to 4 hours from the start of dose administration
[redacted]
[13] The interval between two learning sessions should be in the range of 60 to 90 minutes
[14] No meals should be allowed from 4 h pre-dose to 1hr after infusion start on Day 1
[15] Administered at approximately the same time each dosing day, in the morning or early afternoon at latest.
[16] In case of AE of cystitis or other lower urinary tract event, the PRO Bladder Pain/ Interstitial Cystitis symptom score (BPIC-SS) should be completed
[17] Mandatory visits including for non-responders at End of Core
[18] For non-responders, this visit should be replaced by End of study visit

Table 8-2 Assessment Schedule, Relapse Retreatment

Period	**Retreatment for relapse**																			
Visit Name	**Pre-retreatment**	**Day 1 (1st infusion)**						**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**			
Days	**-14 to -1**	**1**						**2**	**8**	**15**						**22**	**29**			
Time (post-dose)	**-**	**-2h ±1**	**-1h**	**0h**	**20 min & 40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**
Mini International Neuropsychiatric Interview (MINI)	S[2]																			
Physical Examination	S																			
Short Physical Examination		S								S							S			
Electrocardiogram (ECG)[3]			X		X		X	X			X		X		X			X		X
Pulse rate[3]			X		X	X	X	X	X		X		X	X	X	X		X		X
Blood Pressure[3]			X		X	X	X	X	X		X		X	X	X	X		X		X
Respiratory Rate			S		S	S	S	S	S		S		S	S	S	S		S		S
Body Temperature	X										X							X		
Body Weight	X										X							X		
Pregnancy and assessments of fertility	X[4]	S[5]								S[5]							S[5]			
Hematology		X						X	X	X						X	X			
Urinalysis		X						X	X	X						X	X			
Clinical Chemistry	X[11]	X[6]						X	X	X						X	X			
Alcohol Test and Drug Screen [7]		S							S	S						S	S			
Memory Assessment Questions					S[1, 12]								S[1]							S[1]
Oxygen saturation		S[8]								S[8]							S[8]			

Period	**Retreatment for relapse**																			
Visit Name	**Pre-retreatment**	**Day 1 (1st infusion)**						**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**			
Days	**-14 to -1**	**1**						**2**	**8**	**15**						**22**	**29**			
Time (post-dose)	**-**	**-2h ±1**	**-1h**	**0h**	**20 min & 40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**
PK blood collection			X		X[12]		X						X		X					X
[redacted]																				
Montgomery-Asberg Depression Rating Scale (MADRS)	X	X					X	X	X	X					X	X	X			
[redacted]																				

Period	**Retreatment for relapse**																			
Visit Name	**Pre-retreatment**	**Day 1 (1st infusion)**						**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**			
Days	**-14 to -1**	**1**						**2**	**8**	**15**						**22**	**29**			
Time (post-dose)	**-**	**-2h ±1**	**-1h**	**0h**	**20 min & 40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**
[redacted]																				
Study drug administration				X[9]								X[9]							X[9]	
Concomitant medications	X																			
[redacted]																				
Adverse Events	X[10]																			

Period	**Retreatment for relapse**			
Visit Name	**Day 29 (3rd infusion)**		**Day 36**	**End of Retreatment**
Days	**29**		**36**	**43**
Time (post-dose)	**2h**	**4h**	**-**	**-**
Mini International Neuropsychiatric Interview (MINI)				
Physical Examination				
Short Physical Examination				S
Electrocardiogram (ECG)[3]		X		X
Pulse rate[3]	X	X	X	X
Blood Pressure[3]	X	X		X
Respiratory Rate	S	S	S	S
Body Temperature				X
Body Weight				X

Period	**Retreatment for relapse**			
Visit Name	**Day 29 (3rd infusion)**		**Day 36**	**End of Retreatment**
Days	**29**		**36**	**43**
Time (post-dose)	**2h**	**4h**	**-**	**-**
Pregnancy and assessments of fertility				S[5]
Hematology			X	X
Urinalysis			X	X
Clinical Chemistry			X	X[6]
Alcohol Test and Drug Screen [7]			S	S
Memory Assessment Questions				
Oxygen saturation	S[8]			
PK blood collection		X		
[redacted]				
Montgomery-Asberg Depression Rating Scale (MADRS)		X	X	X
[redacted]				
Study drug administration				
Concomitant medications	X			
[redacted]				
Adverse Events	X[10]			

Period	**Retreatment for relapse**			
Visit Name	**Day 29 (3rd infusion)**		**Day 36**	**End of Retreatment**
Days	**29**		**36**	**43**
Time (post-dose)	**2h**	**4h**	**-**	**-**

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Start at 40 min timepoint, subsequently, if memory gaps/ amnesia is present, it must be assessed at least once per hour until resolution
[2] Only M.I.N.I. for MDD
[3] Triplicate
[4] Serum, (FSH test to be performed locally for fertility assessment, see Section 8.4.4)
[5] Urine
[6] In addition for this visit TSH test
[7] Results to be obtained before collection of any clinical and patient questionnaires
[8] Every 15 minutes from pre-dose to 4 hours from the start of dose administration
[9] Administered at approximately the same time each dosing day, in the morning or early afternoon at latest.
[10] In case of AE of cystitis or other lower urinary tract event, the PRO Bladder Pain/ Interstitial Cystitis symptom score (BPIC-SS) should be completed
[11] In case sample is not taken in fasting stage, a repeat chemistry sample must be done on day 1, in fasting condition
[12] Assessment to be completed at the 40 minute timepoint only

8.1 Screening

Screening will be performed while the participant is hospitalized. The duration of the Screening Period is up to 48 hours. In case a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment should be repeated prior to randomization on Day 1. If the repeat value remains outside of the ranges specified in the exclusion criteria, the participant must be screen failed.

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 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered as screen failures. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and 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 serious adverse event during the screening phase (see 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

Participant demographic and baseline characteristic data to be collected on all patients include age, sex, ethnicity. Country-specific regulations should be considered for the collection of demographic and baseline characteristics in the CRF.

Background information that should be reported includes history of previous treatments, relevant medical history, or current medical conditions, diagnosis of disease.

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

8.2.1 Mini International Neuropsychiatric Interview (M.I.N.I.), Version 7.0.2

The Mini International Neuropsychiatric Interview (M.I.N.I.) is a brief structured clinical interview for major psychiatric disorders in DSM-5 and ICD-10. It is divided into diagnostic modules including screening questions corresponding to the criteria for each disorder that allow the physician to assess whether the diagnostic criteria have been met.

The full M.I.N.I. version will be provided to the sites. M.I.N.I will be administered on paper by qualified personnel at screening and at relapse (Table 8-1, Table 8-2)

Module A (Major Depressive Episode), Module B (Suicidality), Module C (Manic and Hypomanic Episodes), Module K (Psychotic Disorders and Mood Disorders with Psychotic Features), Module I (Alcohol Use Disorder), Module J (Substance Use Disorder, Non-Alcohol), Module Y (Borderline Personality Disorder) and Module Z (Suicidality Disorders Classification Interview) should be used for eligibility purposes as defined in the eligibility criteria (Section 5). Other modules should be used, as needed. The results of the interview must be added to the source records to confirm the eligibility criteria.

8.3 Efficacy

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

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] Independent site raters for the MADRS, [redacted] assessments are not allowed to access or review participants safety records and, therefore, they must not provide clinical care for subjects. Clinical care of participants will be performed by the investigator or delegate at the study site who are not MADRS, [redacted]

Whenever possible, all efforts should be made to use the same independent site raters for the MADRS [redacted] 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 interview 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.

8.3.1 The Montgomery Asberg Depression Rating Scale (MADRS), SIGMA version

The Montgomery Åsberg 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.

The structured interview guide for the MADRS (SIGMA) will be used for each administration. The MADRS will be administered electronically by qualified personnel according to Table 8-1.

In this study, the following recall periods will be used: "Last 7 days" and "Since last evaluation", "Since infusion start (last 4 hours)" (see Appendix 6 for more details). For the 4 hours timepoint, the sleep and appetite items will not be assessed (predose scores for these items obtained on the same day will be carried forward).

8.3.2 Appropriateness of efficacy assessments

The Montgomery Åsberg Depression Rating Scale (MADRS) is a standard scale used for registration studies in 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, inner tension, reduced sleep, appetite, concentration difficulties, lassitude, inability to feel, pessimistic 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 (Section 10.1).

To minimize the risk of introducing bias, different site personnel must perform efficacy and safety assessments as described in Section 8.3. The site personnel who performs safety assessments should not communicate any safety findings to the independent site raters.

Table 8-3 Safety Assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. A short physical exam will include the examination of general appearance Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include respiratory rate (source data), BP and pulse measurements (both BP and pulse are to be performed in triplicate). After the participant has been resting supine for ten minutes systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. It is recommended to measure blood pressure following ECG measurements (Section 8.4.3). BP readings are collected at 5-min intervals. The same size cuff and same arm for all

Assessment	Specification
	assessments should be used. The mean of the three BP measurements will be calculated and used for clinical evaluation. 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. Clinically notable vital signs are defined in Section 16.1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in the assessment schedule.

8.4.1 Laboratory evaluations

Clinically notable laboratory findings are defined in Section 16.1.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

At Screening, if a result has not been obtained by the central lab, local lab result will be used to determine patient eligibility. For any laboratory assessments performed locally, an identical sample should also be collected and sent to the central laboratory for analysis to ensure that the values are captured in the central database.

Fasting considerations:

The participants must be fasting at screening in order to collect the fasting glucose. In case the sample was not taken in a fasting 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 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other (absolute value preferred and percent)
Chemistry	Albumin, Alkaline phosphatase, Amylase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate,Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine#, Creatine kinase,Direct Bilirubin, Indirect Bilirubin,Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), C-reactive protein (high sensitivity)
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity, Urobilinogen)
Thyroid	TSH*
Cortisol**	Serum
Alcohol/ drugs of abuse***	Breathalyzer / Dipstick
Pregnancy Test	Serum or urine as per Table 8-1 and Table 8-2

* TSH will be taken as specified in Section 8. In case the result is out of range, T3 and T4 should be measured in addition to TSH at the closest subsequent blood draw. E.g. if the TSH is out of range at Day1 then T3 and T4 should be measured on Day 2.

** Cortisol is to be performed at same timepoint as Chemistry panel.

*** 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 6.2.1.1 and Section 6.2.2) should be further confirmed by the treating physician by means of a clinical

Test Category	Test Name
assessment and data obtained from the patient or his/her relatives. The investigator judgment takes priority in case of contradictory data or results.	
[#] Glomerular Filtration Rate to be calculated based on the Cockcroft-Gault (C&G) formula.	

8.4.2 Oxygen saturation

Pulse oximetry will be used to measure arterial oxygen saturation during the 4-hour observation period on the dosing day. On each 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 study drug administration days, pulse oximetry will be recorded every 15 minutes from pre-dose to 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 subject is referred for appropriate medical care, if clinically indicated.

8.4.3 Cardiac assessments

12-Lead ECG

Electrocardiograms (ECGs) must be recorded after patient rests for 10 minutes rest in the supine position to ensure a stable baseline and heart rate. Thereafter, three ECG should be taken at approximately 2-min intervals (i.e. in triplicate). The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs. The Fredericia QT correction formula (QTcF) should be used for clinical decisions.

Triplicate 12 lead ECGs are to be collected with ECG machines supplied centrally. They 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).

25-hour Holter monitoring

Ambulatory Holter ECG will be recorded for 25 hours for all patients at randomization Day 1 for 25 hours, starting at least one hour before the start of the first intravenous infusion and for approximately 24 hours after the start of the infusion. The Holter device will be removed by the site personnel on Day 2, prior to the participant being discharged from the clinic/hospital if discharge is planned.

Particular care should be taken with the Holter cables to ensure patient safety. Wherever possible, a wireless Holter machine should be used. If the use of a wireless Holter machine is not possible, the site must take appropriate measures to mitigate any risk of self-harming with Holter wires.

Participants should be instructed to avoid strenuous activity that could interfere with the quality of the Holter ECG recording or lead to detachment of ECG skin electrodes during the recording periods.

To avoid food effects on the interpretation of the cardiac assessments participants are not allowed to have food for at least 4 h prior to start of the first intravenous infusion and for 1 hour post start of first infusion (i.e. in total 5 hour fasting period). The meal intake times on Day 1 will be recorded in the CRF to allow assessment of adherence to the food intake recommendation.

8.4.4 Pregnancy, assessments of fertility and contraception requirements

Contraception

During the study (Core and Extension Periods) investigators should ensure that patients in this vulnerable population and at risk of becoming pregnant are regularly reminded of the importance of complying with the highly effective method of contraception.

For WOCBP, highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). 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).

Oral contraception or systemic hormonal contraception (e.g. transdermal or implanted hormonal methods) is not allowed for the purpose of contraception.

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.

WOCBP should follow highly effective contraception methods while taking study treatment and for 1 week after stopping medication (applies to the Core and Extension Period at the time of retreatment).

In addition, the following should be followed in the Extension Period:

- WOCBP that are not eligible for retreatment and enter the 8 weeks Extension Period do not need to adhere to the highly effective methods of contraception.
- WOCBP eligible to receive retreatment for relapse in the Extension Period should not be pregnant prior to the start of the retreatment.
- WOCBP eligible to receive retreatment for relapse in the Extension Period are recommended to stay on the highly effective methods of contraception, to ensure that they remain eligible for retreatment. In case a participant is pregnant at the time of relapse, she would not receive retreatment with MIJ821. A pregnancy test will be performed prior to retreatment to confirm that participants remain eligible for retreatment

Sexually active males must use a condom during intercourse while taking study treatment and for 1 week after stopping study treatment (in the Core and Extension in case of retreatment). 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 as study treatment may involve unknown risks to the fetus if pregnancy were to occur. In addition, male participants must not donate sperm for the time period specified above.

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, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline. Until the results are obtained, highly effective method of contraception is to be used.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. Serum pregnancy testing will be conducted at key visits as described in Table 8-1 and Table 8-2. Additionally, a urine pregnancy test will be required before each study drug infusion. In case of a positive test, the participant must contact the investigator immediately. The positive urine test needs to be confirmed with a serum test. If positive, the participant should not receive further infusions of study drug.

Local pregnancy test and associated results will not be collected on CRF. This should be recorded in the source documents at site.

8.4.5 Safety evaluations related to indication and mode of action

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

- [redacted]
- [redacted]
- Memory assessment using orientation questions

[redacted]

[redacted]

8.4.5.3 Memory Assessment using orientation questions

Memory gaps/ amnesia is an Adverse Event of Special Interest (AESI). Memory Assessment using orientation questions will be recorded as source data according to Table 8-1 and Table 8-2.

Orientation questions will be asked to assess presence or absence of amnesia, as well as any distress for the participant, at defined intervals. It is recommended that the first amnesia assessment occurs at the end of infusion. If memory gaps/ amnesia is present, it should be assessed at least once per hour until resolved. However, if signs of amnesia are observed outside of the recommended time frame, the investigator should conduct the assessment as appropriate based on clinical judgement. The aim is to identify onset and resolution of amnesia. The time of onset and resolution is to 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.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population. Since

MIJ821 is currently at Phase 2 of clinical development, safety evaluation including hematology and blood chemistry assessments are planned every week for close patient monitoring and early detection of any safety signals in the Core and in the retreatment period in case of relapse. In addition, triplicate ECGs will be done at each visit and Holter monitoring for the first 24 hours post-infusion will be implemented to carefully evaluate potential cardiovascular risk.

In case of potential treatment emergent symptoms of cystitis, the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) must be assessed.

[redacted]. Investigators will be trained specifically on identification and appropriate recording of amnesia (Table 8-1 and Table 8-2).

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

To assess suicidality in participants, the following assessments are to be conducted:

- Sheehan Suicidality Tracking Scale (S-STS), clinician-administered version

[redacted]

Sheehan Suicidality Tracking Scale (S-STS) Standard Version, Clinician Rated

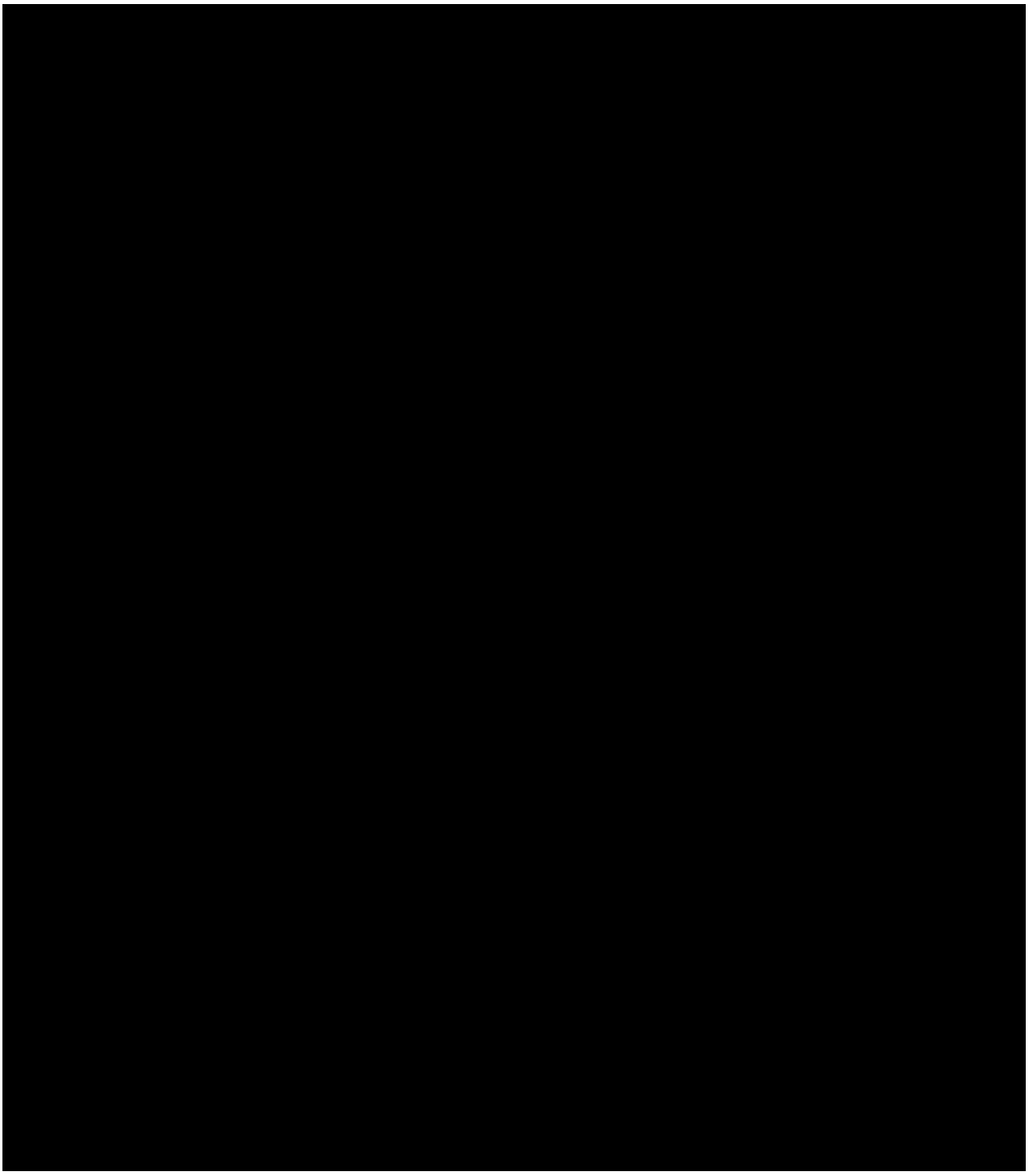
The Sheehan – Suicidality Tracking Scale (S-STS) is designed to assess and monitor suicidality over time. The standard, clinician-rated version of the scale will be used in this trial. The standard version of the scale was designed for use in clinical research studies as a safety assessment measure, to detect treatment emergent suicidality, and as a treatment outcome measure that is sensitive to change. The standard version of the S-STS is a 16-item scale that assesses the seriousness of suicidality phenomena on a Likert-type scale (0–4) ranging from "not at all" (0) to "extremely" (4). It also assesses the frequency of key phenomena and the overall time spent in suicidality (Sheehan et al 2014).

The S-STS will be administered electronically by qualified site personnel according to Table 8-1 and Table 8-2. [redacted]

[redacted]

The validity, reliability and ability to detect change for the S-STS will be assessed. The S-STS will be recorded (audio-recording). Patients will be able to choose to provide or withhold consent for this recording; in the event that patients choose not to be recorded, the rater administering the scale will disable the recording function. Where required by ethic committees, audio recordings will be distorted to prevent identification of individuals and maintain patient privacy. The audio recording(s) will not be transferred to Novartis. Qualified personnel at an external vendor will perform an independent review of selected S-STS assessments based on the audio-recording(s). The details of these psychometric analyses and related procedures will be described in a separate statistical analysis plan and reported in a separate report.

[redacted]



8.5.3 Pharmacokinetics

Pharmacokinetic (PK) samples will be collected at the time points defined in the Assessment Schedule (Table 8-1). All times defined for PK sample collection refer to the start of infusion defined as time 0 h. Instructions are outlined in the central laboratory manual regarding sample collection, numbering, processing and shipment. Refer to Section 8.5.4.1 for information regarding the potential use of residual samples.

It has to be emphasized, that all PK samples **must be collected from the contralateral arm of the infusion site**.

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

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

Pharmacokinetic analytical method(s)

Concentration in plasma of MIJ821 will be determined by a validated LC-MS/MS method. The lower limit of quantification (LLOQ) is considered to be 0.1 ng/mL MIJ821 in plasma. 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.

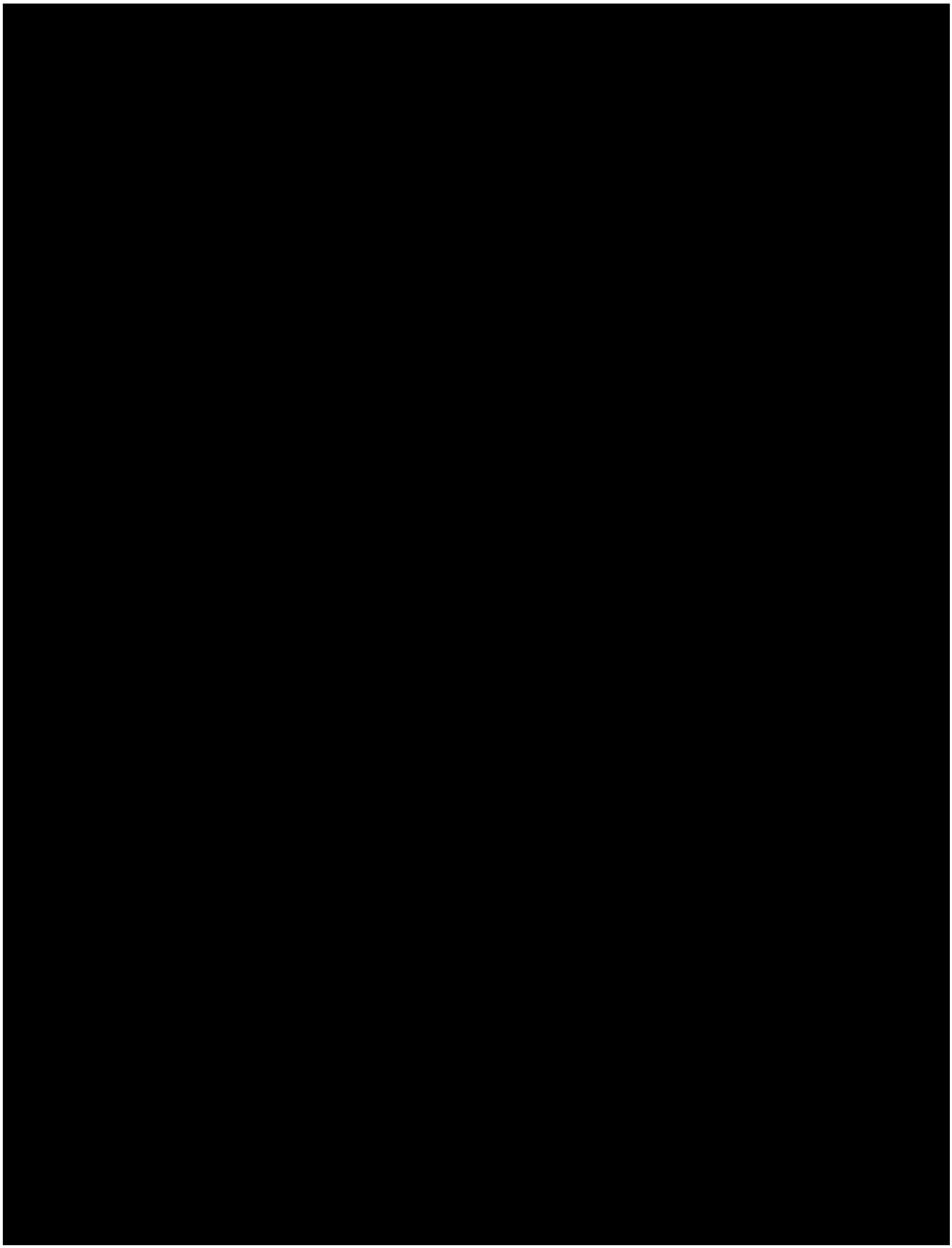
Pharmacokinetic parameters

If data permit, the following pharmacokinetic parameters of MIJ821 will be determined after the first infusion using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8 or higher):

Following first infusion, AUClast, Cmax, Tmax, and if feasible T1/2 will be determined from the plasma concentration-time data. If PK data allow, secondary PK parameters will be estimated like AUC0-24h (or other AUC values across a defined period), AUCinf, CL, Vz (but not limited). Following all other infusions, Cmax and Tmax will be determined.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for the secondary PK parameters like T1/2, AUCinf, Vz and CL, or other parameter dependent on estimation of the terminal phase.

[redacted]



9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

Discontinuation of study treatment may or may not include study drug infusion interruption, i.e. shortening of the infusion to less than 40 minutes. If the duration of an infusion is shortened, the next planned infusion should be planned to be administered for the full 40 minutes. If there is a concern that the participant cannot tolerate the full duration of the infusion the investigator should consider permanent discontinuation of study treatment.

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

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.2.2
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding
- Severe hypersensitivity reaction such as anaphylaxis
- Adverse events (including AESI, see Section 10.2.5), abnormal laboratory values or abnormal test result that indicate a safety risk to the participant
- Lack of study treatment effect based on Investigator’s judgement
- Patients meeting the discontinuation criteria for liver laboratory triggers or renal alert criteria as defined in Table 16-4 and Table 16-5

- Study treatment should also be discontinued for any one of the following treatment-emergent events:
  - Absolute QTcF > 500 msec, confirmed by repeat ECG measurements
  - Resting heart rate < 30 or > 120 bpm
  - QRS > 120 msec and increase > 25% from Baseline (Day 1)
  - Sustained ventricular tachycardia lasting 30 sec or more, ventricular fibrillation, or any hemodynamically compromising cardiac arrhythmia
  - New complete heart block (Grade III AV block) or Second degree AV block Mobitz type II
  - Post-dose systolic blood pressure of ≥200 mmHg and/or the DBP is ≥120 mmHg confirmed by triplicate reading (at least one value should confirm the blood pressure increase above the defined thresholds).

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2). Where possible, they should return for the assessments indicated in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section.

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

Following study treatment discontinuation (no further infusions planned), participants should be followed for two months beyond the 6 week Core Period (Follow-up Period).

Participants who discontinue study treatment during the Core Period should return at every scheduled visit until the End of the 6 week Core Period. The list of assessments should be kept as planned with the following exceptions: ECG and vital signs to be measured (triplicates required), no PK sampling collection, and all assessments that are repeated several times in one day should be done only once [redacted] Participants will then enter the two months Follow-up Period.

Participants who discontinue study retreatment during the Extension Period should return for the End of Relapse visit and subsequently enter the two month Follow-up Period.

If an onsite visit is not possible, then telephone visits should be conducted and collected at minimum the following:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because the treatment code has been broken, please refer to Emergency breaking of the treatment code Section 6.6.3.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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 his/her consent and record this information.

In situations in which consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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

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

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

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 or withdraw, 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.

9.1.4 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 prematurely withdrawn. 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.

9.2 Study completion and post-study treatment

All randomized and/or treated participants should enter, at minimum, an 8 weeks Follow-up Period after the End of Core Period, or they will enter the Extension Period of 52 weeks as defined in Section 3.3.

Study completion is defined as when the last participant finishes their Study Completion visit at the End of the Extension Period or the eight weeks Follow-up, as applicable. Any repeat assessments associated with this visit should be documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision, as communicated, should be documented.

If the participant cannot be reached, documentation of attempts to contact the participant should be recorded in the source documentation.

Please also refer to Section 10.1.3 for the requirements for SAE reporting.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a 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 adverse events.

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

The occurrence of adverse events must be sought by non-directive questioning of the 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 or reports [redacted]

Adverse events 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. In relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of MDD) 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 if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes an SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.
   - Interruption of intravenous infusion (prior to the complete 40 min duration)
   - Drug interruption/withdrawal (no further intravenous infusions)
6. Its outcome (e. g. 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 throughout the study until the End of Study 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 Investigator's Brochure (IB).

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

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

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

with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

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 an 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) (ICH-E2D).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or if related to a logistic/administrative reason (e. g. IV infusion-related and/or required observation period as part of the protocol requirements)
  - 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) (ICH-E2D).

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 the End of Study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Relapse (Extension Period)

For a relapse episode that is unusually severe or unexpected and warrants specific notification, an SAE form must be completed and submitted according to the SAE reporting procedures described in Section 10.

AEs Commonly Seen in the Patient Population

For this study in patients with acute MDD who have suicidal ideation with intent the following are considered the anticipated AEs:

- Suicidal thinking, ideation, and behavior
- Mood disturbances, including depression/worsening of depression, depressed mood

These events will be captured on the eCRF and in the database, and will be reported to the sponsor as described in Section 10.1.1. If the event meets the criteria for an SAE, the SAE must also be immediately reported to Novartis per the SAE reporting requirements described in Section 10.1.3. As the unblinding of single SAEs for the above events, for SUSAR reporting, would not increase the understanding of safety, and may impact the integrity of the blinded nature and analysis for this study, therefore they would not be unblinded during the course of the study, even if considered "related" to study treatment by the reporting investigator, and will not be reported on expedited basis to regulatory authorities.

The DMC will perform reviews of all adverse events including the AEs commonly seen in the patient population at an aggregate level. The DMC is independent of the sponsor's study team and will provide recommendation to the sponsor's study team in case a possible causal association of the study drug is noted, or an imbalance is noted for the adverse event in comparison to Placebo. If based on this aggregate review by the DMC, it is determined that an anticipated event is possibly related to study drug, Novartis will report these events in an expedited manner to the Health Authorities, as Aggregate Finding Safety Reports.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

Randomized OR Treated Participants: SAEs collected between time participant signs ICF until the End of Study 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 CMO&PS (Novartis Chief Medical Office and Patient Safety) 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. The exception to this rule are mentioned above, which includes the SAEs commonly seen in the study population. (EMA 2013, EMA 2015)

10.1.4 Pregnancy reporting

When pregnancy occurs in a participant in the study, the study treatment must be discontinued, and appropriate pregnancy follow-up should be initiated. The participant should be encouraged to stay on the study and continue the study assessments. All assessments that are considered as a risk during pregnancy must not be performed. The participant may continue all other protocol assessments.

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her 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 CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

In this study in case of partner pregnancy, the pregnancy follow-up is the same as for a female patient pregnancy described above.

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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 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

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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

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 Section 16.2 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 and Table 16-4. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and GGT) 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. For unscheduled laboratory assessments performed locally, an identical sample should also be sent to the central laboratory for analysis and capture in the central database. 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, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event

- Thorough follow-up of the liver event
  - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and 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, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after 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 Table 16-5

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
- Study treatment interruption
- Discontinuation of the investigational drug, if appropriate (refer to Section 9.1.1)

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:

- Consider study treatment interruption
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study treatment.
- Discontinue the investigational drug if absolute QTcF > 500 msec, confirmed by repeat ECG measurements as also described in Section 9.1.1

Post dose blood pressure monitoring:

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

At 2 hours postdose, 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 patients with SBP ≥180 mmHg but <200 mmHg and/or the DBP is ≥110 mmHg but <120 mmHg, further dosing should be interrupted (no subsequent IV infusion given) and the subject should be referred to a cardiologist, or other specialist for a follow-up assessment.

After the assessment by a cardiologist, or other specialist, if recommended by the referring doctor and considered appropriate according to the clinical judgment for the subject to continue in the study, the subject may continue with further dosing only if the predose blood pressure at the next scheduled visit is within the acceptable range.

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

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 other 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

[redacted] 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.

Lower urinary tract AEs

In case of Adverse events of cystitis or other lower urinary tract event the BPIC-SS will need to be completed. It is a patient questionnaire that has been developed to assess bladder related symptoms (pain, discomfort, pressure, excessive urinary frequency etc.) (Humphrey et al 2012). It is an eight item scale assessing symptoms in the past 7 days, that are scored and when summed create a total ranging from 0 to 38 and will be entered directly in the eCRF as an AE CRF page.

10.2.6 Data Monitoring Committee

This study will include a 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, 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 of any significant safety finding(s) are observed by the DMC. In the event 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 recommendations of the DMC will be documented and will be made available to 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.

10.2.7 Steering Committee

The Steering Committee (SC) is established as group of external experts in the fields of psychiatry with profound knowledge and experience in Major Depressive Disorder (MDD) and Suicidality and in clinical research on MDD. These experts may participate in the trial as investigators, but will not be members of the independent DMC.

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 clinical trial team, 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

Designated investigator staff will enter the data required by the protocol into the 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 Electronic Data Capture (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 for 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.

All clinical scales administered by the clinician or self-reported by the participant will be collected on an eSource (Virgil® tablet) provided by the vendor who will also manage the database. The database will be sent electronically to Novartis with the exception of the audio recordings.

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 the analysis. 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. 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, electrocardiograms, 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. The investigator must also keep the original informed consent forms 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. There will be an unblinded interim analysis performed when all participants completed Day 57 (2 weeks Follow-up visit) including early withdrawers. The purpose of this interim analysis to select the optimal dose of MIJ821, based on all efficacy, safety, and PK data of MIJ821 doses/regimens and placebo up to and including Day 57. The dose-response relationship will be established based on the primary estimand by method of Multiple Comparison Procedure – Modelling (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: n, 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 at least one dose of randomized treatment. Participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first actual treatment received if the randomized/assigned treatment was never received due to dispensing error.

12.2 Participant demographics and other baseline characteristics

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

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

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

12.3 Treatments

The Safety set will be used for the analyses below.

The number of investigational drug administered will be summarized by treatment group for Core Period and Extension Period separately. The duration of infusion as well as interruption/discontinuation reasons (if applicable) should be collected and listed.

The initial SoC and/or the SoC adjustment during study should be collected and summarized.

The concomitant medications/therapies which have potential confounding effects will be summarized according to Anatomical Therapeutic Chemical (ATC) classification system by treatment group and listed. The prohibited medication and rescue medications will be analyzed similarly.

Categorical data will be summarized as frequencies and percentages.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary clinical question of interest targeting the primary objective is: What is the effect of the MIJ821 versus placebo in change from baseline in MADRS total score at 24 hours post first dose administration, in conjunction with SoC, in participants with MDD who have suicidal ideation with intent, while accounting for intercurrent events (IEs) with potential confounding effects and IEs leading to study discontinuation prior to the 24 hours assessment.

This section defines the primary analysis for the primary estimand. The related sensitivity analyses, supplementary analyses as well as supportive analysis will be detailed in the SAP.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary estimand, defined below, quantifies the treatment effect of MIJ821 at 24 hours post first dose administration while accounting for intercurrent events (IEs) with potential confounding effects and IEs leading to study discontinuation prior to the 24 hours assessment.

Population: Participants with MDD who have suicidal ideation with intent.

Variable: Change from baseline in MADRS total score at 24 hours post first dose administration

Treatment:

- Placebo every other week
- MIJ821 0.0048 mg/kg every other week
- MIJ821 0.016 mg/kg every other week
- MIJ821 0.048 mg/kg every other week
- MIJ821 0.16 mg/kg every other week
- MIJ821 0.048 mg/kg single infusion with two subsequent placebo dosages given every other week
- MIJ821 0.16 mg/kg single infusion with two subsequent placebo dosages given every other week

On the top of ongoing pharmacological antidepressant SoC treatment. Dosage titration or adjustments of standard-of-care antidepressant treatment occurred during the first 2 weeks of double-blind treatment are allowed, if needed, with dosages maintained thereafter during the Core Period.

Intercurrent Events (IEs) (not limit to):

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

- Intake or changes in concomitant medications/therapies other than SoC which have potential confounding effects
- Intake of prohibited medications
- Intake of rescue medications
- Pandemic related IEs

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

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

Participants who took prohibited medications/prohibited therapy treatment, rescue medications, or concomitant medications other than allowed SoC will continue stay in the study and be treated if allowed and will be assessed as scheduled.

Population Level Summary: Treatment difference of variable means between study drug and placebo

[redacted]

[redacted]

[redacted]

12.4.3 Handling of remaining intercurrent events of primary estimand

Table 12-1 Potential intercurrent events, estimand strategy and data handling

Intercurrent Event Prior to 24 hour Assessment	Estimand Strategy	Data Handling
Intake of concomitant medications other than allowed SoC, which have potential confounding effects	hypothetical strategy	Observed values, if any, after the IE will be excluded. For missing and excluded values, multiple imputation (MI) will be performed based on missing at random (MAR) within the same treatment arm.
Intake of prohibited medications/Use of prohibited therapy treatment	hypothetical strategy	Observed values if any will be excluded. For missing and excluded values, MI will be performed based on missing at random (MAR) within the same treatment arm.
Intake of rescue medications	hypothetical strategy	Observed values if any will be excluded. For missing and excluded values, MI will be performed based on missing at random (MAR) within the same treatment arm.
Pandemic Related IEs	hypothetical strategy	Observed values if any will be excluded. For missing and excluded values, MI will be performed based on missing at random (MAR) within the same treatment arm.
IEs leading to study discontinuation prior to the 24 hour assessment due to: ● Adverse events (AE) ● Lack of efficacy ● Other reasons for study treatment discontinuation	treatment policy strategy	Observed values if any will be included. For missing values, for placebo arm, MI will be performed based on MAR within the placebo arm; for active arms, MI will be performed based on jump to reference (placebo) borrowing from placebo participants.

Participants who took prohibited medications/prohibited therapy treatment, rescue medications, or concomitant medications other than allowed SoC will continue stay in the study and be treated if allowed and be assessed as scheduled.

12.4.4 Handling of missing values not related to intercurrent event

The imputation of permanent missing observations at 24 hours due to study discontinuation has been defined in Section 12.4.3

For all analyses, imputation of intermittent missing observations before treatment discontinuation will be carried out following a MAR mechanism for all treatment arms.

12.5 Analysis of secondary endpoints/estimands

Not applicable

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

To assess the effect of MIJ821 on sustained response and remission, following secondary efficacy endpoints will be evaluated:

- Proportion of participants meeting response criteria (≥50% reduction from baseline in MADRS total score) over time in the Core Period.
- Proportion of participants meeting criteria for sustained response (≥50% reduction from baseline in MADRS total score sustained for a period of at least four weeks) in the Core Period
- Proportion of participants meeting remission criteria (MADRS total score of ≤12) over time in Core Period
- Proportion of participants meeting criteria for sustained remission (MADRS total score of ≤12 sustained for a period of at least four weeks) in the Core Period
- Proportion of participants meeting criteria for relapse over all randomized population over fixed period in the Extension Period
- Proportion of relapsing participants meeting response criteria or remission criteria after the first infusion of MIJ821 retreatment in the Extension Period

12.5.2 Safety endpoints

The safety and tolerability of MIJ821 will be evaluated by the number and severity of adverse events occurring during the first dose to 2 weeks post last dose of Core Period (or before retreatment if it's earlier than 2 weeks). For relapsed participants who take re-treatment of MIJ821, the safety and tolerability of retreatment will be evaluated by adverse events occurring from the start of retreatment to 2 weeks post last dose in Extension Period.

Clinical significant findings from laboratory test, physical examination, vital signs, 12-lead ECG, Holter ECG and additional safety scales will be reported as adverse events and analyzed as such.

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

Adverse events

TEAEs are defined as adverse events starting or worsening after the first dose of study medication up to 2 weeks post the last dose. For relapsed participants who receive retreatment of MIJ821 in Extension Period, adverse events starting after 2 weeks post the last dose of Core Period up to the start of retreatment will not be counted as TEAEs. The number (and percentage) of participants with TEAEs will be summarized as followed:

- 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 permanent discontinuation.

The number (and proportion) of participants with adverse events of special interest (as defined in Section 10.2.4) will be summarized by treatment.

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

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

Abnormal vital signs data will be listed by treatment group, participant, and visit/time point if ranges are available

12-lead ECG

Summary statistics will be provided by visit/time point and treatment for ECG parameters. Categorical Analysis of ECG interval data based on the number of participants meeting or exceeding predefined limits will be presented by visit/time point.

Abnormal ECG data will be listed by treatment group, participant, and visit/time point if ranges are available.

Holter ECG

The number and proportion of participants meeting abnormal Holter ECG interval criteria will be summarized.

Clinical laboratory evaluations

Summary statistics will be provided by visit/time point and treatment. Shift tables using the low/normal/high/ (low and high) classification based on predefined limits will be used to compare baseline to the worst on-treatment value. Notable abnormal laboratory data will be listed by treatment group, participant, and visit if limits are available.

12.5.3 Pharmacokinetics

MIJ821 plasma concentrations will be expressed in mass per volume. The plasma concentrations will be listed by treatment, subject number, and visit/sampling time point. Descriptive summary statistics will be provided by treatment 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 mean (arithmetic and geometric), SD, CV (arithmetic and geometric), 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.

Pharmacokinetic parameters will be calculated as described in Section 8.5.3 and will be listed by treatment and subject number. Descriptive summary statistics of pharmacokinetic parameters will include mean (arithmetic and geometric), SD, and CV (arithmetic and

geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

The dose proportionality of MIJ821 for PK parameters such as Cmax and AUClast (or other AUCs) will be explored for PK parameters collected after the 1st infusion. The selection, which of the AUC values will be used, depends on the determinability of plasma concentration above LLOQ and the estimation of comparable AUC values across the cohorts.

[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)
AUC0-24h	Area under the curve from time zero to 24 h after start of infusion (mass x time x volume-1)
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	The total body clearance of drug from the plasma (volume x time-1)
Vz	The apparent volume of distribution during terminal phase (volume)

[redacted]

[redacted]

12.7 Interim analyses

One interim analysis will be performed when all participants completed Day 57 (2 weeks follow-up visit). All data captured up to Day 57 (2 weeks follow-up visit) will be analyzed according to the plan. The optimal dose will be identified with the dose-response relationship built up by MCP-Mod, as well the sustained efficacy effect, safety profile and PK of each MIJ821 dose and regimen.

This unblinded interim analysis will be conducted by study team. The individual unblinded data will be kept blinded to investigators and participants until final database lock.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

With the randomization ratio of 2:1:2:2:2 for the biweekly dosing arms, the sample size of 27:14:27:27:27 for placebo, MIJ821 0.0048 mg/kg, MIJ821 0.016 mg/kg, 0.048 mg/kg and 0.16 mg/kg, will provide about 80% power to detect a dose-response signal [to reject the null hypothesis of a flat dose-response curve where all MIJ821 dose means are equal to the placebo mean] for the biweekly dosing arms in change from baseline in MADRS at 24 hour using MCP-Mod methodology at the one-sided alpha = 0.05 level. Since MIJ821 0.0048 mg/kg is potentially non-effective, the sample size for this arm is chosen to be 50% of other arms and is sufficient for establishing the dose-response curve.

The 6 candidates DR curves (2 Emax, 4 Sigmoid Emax) for power calculation are defined in Section 12.4.2. [redacted]

For the two single infusion arms of 0.048 mg/kg and 0.16 mg/kg, to maintain the same precision as for the biweekly dosing arm vs placebo, 27 participants per arm are needed. In total the study

needs 177 participants. Assuming a 10% dropout rate, approximately 195 pts in total (15 pts for 0.0048 mg/kg and 30 pts for the remaining 6 treatment groups) will be randomized.

All treatment arms (including both regimen) will be included in the MCP-Mod for the primary analysis which will provide about 92% power to detect a dose-response signal in change from baseline in MADRS at 24 hour using MCP-Mod at the one-sided 0.05 level.

12.8.2 Secondary endpoint(s)

Section 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 patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g.; Clinicaltrials.gov, EudraCT, etc.).

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of 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.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Table 16-1 Clinically notable values for vital signs and weight changes

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
Weight	Baseline weight (kg)	increase of ≥ 7% decrease of ≥ 7%

bpm= beats per minuteClinically notable laboratory values

Notable laboratory values will be specified in the laboratory manual with specific alert values. Both the Novartis clinical team and the investigator will be notified for all types of alerts.

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 If ALT, AST and total bilirubin normal at baseline:	● ALT or AST > 5 × ULN ● 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 > 300 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 (ULN)

Table 16-3 Follow up requirements for liver laboratory triggers with liver symptoms

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	● **No change to study treatment** ● Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms.
If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	● **Interrupt study drug** ● Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms. ● Initiate close monitoring and workup for competing etiologies. ● Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-4 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Biliruin (isolated)		
>1.5 – 3.0 ULN	● Maintain treatment ● Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	● Interrupt treatment ● 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[c] 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	● Discontinue the study treatment immediately ● Hospitalize the participant	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until

Criteria	Actions required	Follow-up monitoring
	● Establish causality ● Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	● Consider study treatment interruption or discontinuation ● Hospitalization if clinically appropriate ● Establish causality ● Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

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

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 drug interruption or discontinuation unless other causes are diagnosed and corrected ● Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	● Consider causes and possible interventions ● Assess serum albumin & serum total protein ● Repeat assessment to confirm ● Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Assess & document ● Repeat assessment to confirm ● Distinguish hemoglobinuria from hematuria ● Urine sediment microscopy ● Assess sCr ● Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation ● Consider bleeding disorder

+ Corresponds to KDIGO criteria for Acute Kidney Injury

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

Table 16-6 Renal Event Follow Up

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in the CRF ● Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells ● Blood pressure and body weight ● Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid ● Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
Monitor patients regularly (frequency at investigator's discretion) until - ● Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or ● Event stabilization: sCr level with ±10% variability over last 6 months or protein- creatinine ratio stabilization at a new level with ±50% variability over last 6 months. ● Analysis of urine markers in samples collected over the course of the DIN event

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
Azithromycin	Zithromax and others	known
Bepridil	Vascor	known
Cesium Chloride	Energy Catalyst	known
Chloroquine	Aralen	known
Chlorpromazine	Thorazine and others	known

Generic name	Brand name	TdP Risk
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
Quinidine	Quinaglute and others	known
Roxithromycin	Rulide and others	known
Sevoflurane	Ultane and others	known
Sotalol	Betapace and others	known

Generic name	**Brand name**	**TdP Risk**
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

17 Appendix 6. Recall Periods

Period	**Screening**	**Core Period**																		
Visit Name	**Screening**	**Day 1 (1st infusion)**							**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**		
Days	**-2 to -1**	**1**							**2**	**8**	**15**						**22**	**29**		
Time (post-dose)	**-**	**-2h ±1[2]**	**-1h**	**0h**	**20min**	**40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**
MADRS	Last 7 days with euthymic baseline	Last 7 days						Since infusion start (last 4 hrs)	Since last evaluation	Last 7 days	Last 7 days					Since infusion start (last 4 hrs)	Last 7 days	Last 7 days		
[redacted]																				

Period	**Screening**	**Core Period**					
Visit Name	**Screening**	**Day 1 (1st infusion)**	**Day 2**	**Day 8**	**Day 15 (2nd infusion)**	**Day 22**	**Day 29 (3rd infusion)**
Days	**-2 to -1**	**1**	**2**	**8**	**15**	**22**	**29**
[redacted]							

Period	**Core Period**					**Extension**			**End of Study**
Visit Name	**Day 29 (3rd infusion)**			**Day 36**	**End of Core**	**2 weeks F/U[16]**	**4 weeks F/U[16]**	**Every 4 weeks[17]**	**End of Study**
Days	**29**			**36**	**43**	**57**	**71**	**99**	**-**
Time (post-dose)	40min	2h	4h	-	-	-	-	-	-
MADRS			Since infusion start (last 4 hrs)	Last 7 days	Last 7 days	Last 7 days	Last 7 days	Last 7 days	Last 7 days
[redacted]									

Period	**Core Period**					**Extension**			**End of Study**
Visit Name	**Day 29 (3rd infusion)**			**Day 36**	**End of Core**	**2 weeks F/U[16]**	**4 weeks F/U[16]**	**Every 4 weeks[17]**	**End of Study**
Days	**29**			**36**	**43**	**57**	**71**	**99**	**-**
Time (post-dose)	40min	2h	4h	-	-	-	-	-	-
[redacted]									

Period	**Retreatment for relapse**																				
Visit Name	**Pre-retreatment**	**Day 1 (1st infusion)**						**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**			
Days	**-14 to -1**	**1**						**2**	**8**	**15**						**22**	**29**			
Time (post-dose)	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**
MADRS	Last 7 days	Last 7 days with euthymic baseline					Since infusion start (last 4 hrs)	Since last evaluation	Last 7 days	Last 7 days					Since infusion start (last 4 hrs)	Last 7 days	Last 7 days			
[redacted]																				

Period	**Retreatment for relapse**																				
Visit Name	**Pre-retreatment**	**Day 1 (1st infusion)**						**Day 2**	**Day 8**	**Day 15 (2nd infusion)**						**Day 22**	**Day 29 (3rd infusion)**				
Days	**-14 to -1**	**1**						**2**	**8**	**15**						**22**	**29**				
Time (post-dose)	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**24h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**	**2h**	**4h**	**-**	**-2h ±1**	**-1h**	**0h**	**40min**
[redacted]																				

Period	**Retreatment for relapse**			
Visit Name	**Day 29 (3rd infusion)**		**Day 36**	**End of Retreatment**
Days	**29**		**36**	**43**
Time (post-dose)	**2h**	**4h**	**-**	**-**
MADRS		Since infusion start (last 4 hrs)	Last 7 days	Last 7 days
[redacted]				