NOVARTIS

Clinical Development

MIJ821

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

Statistical Analysis Plan (SAP)

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14-Jun-2021	First version	
30-Jun-2023	Amendment 1 final	
	Added MIJ821 PK analysis in CSR SAP since it's one of secondary endpoints	Section 2.1.3 Analysis sets Section 2.7 PD and PK/PD analyses
	Defined Randomized Set for population description; defined Extension Set for follow-up data analysis	Section 2.1.3 Analysis sets
	For the supplementary estimand, changed the missing data imputation approach from J2R to MAR under treatment policy. Because MIJ821 will sustained effect after 1st dosing for a while, so J2R is scientifically inappropriate.	Section 2.4.5 Supplementary analysis
	Removed summary of MADRS, [redacted]	Section 2.4.6 Supportive analysis Section 2.10.1 Effect on depression mood Section 2.10.2 Effect on suicidality
	Added KM analysis for time to relapse; Added logistic regression model with firth method as the alternative model to repeated logistic regression model if not converged due to zero count	Section 2.5.2 Statistical hypothesis, model, and method of analysis Section 2.10.2 Effect on suicidality

Date	Major updates and reason	Section and title impacted (Current)
	Added the summary of time to onset and time to resolution for AESIs if onset on dosing day, and since most recent dose.	Section 2.6.1.1 Adverse events (AEs)
	Added the change from most recent dose in terms of ECG parameters; Removed summary for holter due to data is not supportive for it	Section 2.6.4.1 ECG and cardiac imaging data
	Added the change from most recent dose for SBP/DBP	Section 2.6.4.2 Vital Signs
	[redacted] [redacted]	[redacted]
	[redacted]	[redacted]

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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
[redacted]	
BDNF	Brain-Derived Neurotrophic Factor
BP	Blood Pressure
BPIC-SS	Bladder Pain/Interstitial Cystitis Symptom Score
[redacted]	
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CRS	Case Retrieval Strategy
CSR	Clinical Study Report
CTT	Clinical Trial Team
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DBS	Deep brain stimulation
DMC	Data Monitoring Committee
DR	Dose Response
[redacted]	
ECT	Electroconvulsive therapy
ECG	Electrocardiogram
ENS	Extension Set
FAS	Full Analysis Set
IA	Interim Analysis
IRT	Interactive Response Technology
LLOQ	Lower Limit of Quantification
LoE	Lack of Efficacy

MADRS	Montgomery–Asberg Depression Rating Scale
MAOIs	Monoamine Oxidase Inhibitors
MAR	Missing At Random
MCP-Mod	Multiple Comparison Procedure-Modelling
MDD	Major Depression Disorder
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measures
[redacted]	
NMDA	N-Methyl-D-Asparate
PD	Pharmacodynamic(s)
PD	Protocol Deviation
[redacted]	
PK	Pharmacokinetic(s)
PKS	PK Analysis Set
PoC	Proof of Concept
PRO	Patient Reported Outcomes
PT	Preferred Term
QTcF	QT interval corrected by Fridericia's formula
RAS	Randomized Set
RTS	Retreatment Set
S-STS	Sheehan Suicidality Tracking Scale
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
[redacted]	
SMQ	Standardized MedDRA Query
SNRI	Serotonin-norepinephrine reuptake inhibitor
SoC	Standard of Care
SOP	Standard Operating Procedure
SSRI	Selective serotonin-reuptake inhibitor
TCA	Tricyclic antidepressant
TEAEs	Treatment-Emergent Adverse Events
TFL	Tables, Figures and Listing
TMS	Transcranial Magnetic Stimulation
VNS	Vagus nerve stimulation
WHO	World Health Organization

1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analysis according to Section 12 of the study **Protocol v01** for MIJ821A Study CMIJ821A12201 dated **Jun 01, 2021** and along with any additional analyses, specifications or deviations from the protocol planned.

The scope of this plan includes the primary, secondary, [redacted], which will be executed by Novartis internal statisticians and programmers, if not specified differently. Those analyses will be reported in the CSR.

1.1 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 40-min infusion in addition to comprehensive standard of care (SoC) for the rapid reduction of the symptoms of major depression disorder (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 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 hours), a Double-blind Core Period (6 weeks) and Extension Period (up to 52 weeks).

Approximately 195 participants will be randomized to Double-blind Core Period via Interactive Response Technology (IRT) in a blinded manner. There is no stratification factor considered in randomization.

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. Participants who complete the Core Period on study treatment (with Day 29 infusion completed) and are classified as responder or remitters at the end of Core Period, will be eligible for a retreatment course of 6 weeks in case of relapse. The details are defined in protocol Section 3.2 and 3.3.

The primary analysis will be performed at end of Core Period and at the end of study. There will be an unblinded interim analysis (IA) performed when all participants completed the 2 weeks follow-up visit post Core Period. The purpose of this IA is to select the optimal dose of MIJ821 for Phase 3.

1.2 Study objectives and endpoints

Table 1-1 Objectives and Related Endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Core:** To investigate 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 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 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 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 Core Period • Proportion of participants meeting criteria for relapse over all randomized population over fixed period in Extension Period • Proportion of relapsing participants meeting response criteria or remission criteria after the first infusion of MIJ821 retreatment in 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
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	

[redacted]

1.2.1 Primary Estimand(s)

The primary clinical question of interest is: what is the effect of the MIJ821 versus placebo in conjunction with pharmacological 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 with potential confounding effects and intercurrent events leading to study discontinuation prior to the 24 hours assessment.

The primary estimand is described by the following attributes with further details in Section 2.4.1:

- Population: Patients with MDD who have suicidal ideation with intent.
- 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 IV 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.
- Handling of intercurrent events prior to MADRS assessment at 24 hours:
    - 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
    - Intercurrent events related to pandemic: hypothetical strategy
    - Intercurrent events leading to study discontinuation due to Adverse events (AEs), lack of efficacy or other reasons: treatment policy strategy
- The summary measure: difference in variable means between treatments

2 Statistical methods

2.1 Data analysis general information

This document describes the analysis plan for unblinded IA at the end of Core Period and the final analysis at the end of study. When the last participant completed 2 weeks' follow-up visit (Day 57), data collected up to the cutoff date will be included at the unblinded IA. The main analysis of unblinded IA will focus on Core Period as well as time to relapse in Extension Period.

At end of the study, data collected mainly from Extension Period will be analyzed. The full scope of analysis will be performed by Novartis.

The analysis for the requirement of regular Data Monitoring Committee (DMC) meetings will be performed by an independent statistical analysis team outside of Novartis (CRO). The process is detailed in the DMC Charter and a separated SAP for DMC.

[redacted].

Statistical analysis will be performed using SAS® statistical software (SAS Institute, Cary, NC, USA.) version 9.4 or higher, and R version 3.5.3 or higher.

Unless otherwise specified, summary tables/listings/figures will be presented for each treatment arm in the respective analysis set. The pooling analysis of treatment arms is defined in Section 2.4.1. In general, data of interest will be listed by treatment arm and by country/center number/subject id (/period/visit wherever applicable). Summary tables and figures by visit will be displayed for Core Period and Extension Period separately. For participants who are retreated during Extension Period, data under Retreatment Period will be analyzed and displayed separately (see definition in Table 2-1).

In general, assessments at scheduled visits will be analyzed. The assessment schedule is defined in protocol Table 8-1 and Table 8-2, thus will not be repeated in this SAP.

Categorical data will be presented as frequencies and percentages. For continuous data, the number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum will be presented.

General information on treatment arm handling, decimal places and other output-related information will be specified in tables, figures and listing (TFLs) shells accompanying this analysis plan.

2.1.1 General definitions

Study drug (treatment)

Study drug (treatment) referred in this document will be MIJ821 or Placebo.

Randomization (Enrollment) Date

Randomization (Enrollment) Date is the date on which a participant is assigned to one of the treatments through IRT in Core Period.

Date of first dose

The date of first dose is the date on which a participant is administered the first infusion of study drug, which maybe on the same day or after the randomization date. For participants who are randomized but never dosed with double-blind study drug after randomization, the date of first dose is considered missing.

Date of last dose

The date of last dose is the latest infusion date throughout study, including Extension Period for participants who take retreatment for relapse.

Day 1

Day 1 is defined as the first dose date. For participants who are randomized but not dosed after randomization, the Study Day 1 is defined as the date of randomization.

Study day

Study Day is defined as the number of days from Study Day 1.

Before Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1)

On or after Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1) + 1

Therefore the day prior to Study Day 1 is -1.

Day(s) since start of retreatment is defined as the number of days from the first dose date of retreatment. It will be calculated for assessments performed during retreatment period by

Date of interest – Date of first dose of retreatment + 1

Baseline

A baseline value refers to the last evaluable measurement prior to the first dose, irrespective of re-screening. In this case, baseline values will be the values obtained predose on first dosing day or on an earlier visit (scheduled or unscheduled) which is the closest to the first dosing day, if the assessment was not done on the first dosing day. In case of multiple assessments on the same day, the last valid one will be considered.

Baseline of Retreatment

For participant who take retreatment during Extension Period, the baseline for retreatment assessments will be the last evaluable measurement prior to the first dose of retreatment. It will be the measurement obtained predose on the first day of retreatment, or the last valid assessment which is closest to start of retreatment.

2.1.2 Analysis period and visit remapping

All study data of participants will be grouped into Core Period and Extension Period according to Table 2-1. For those who take retreatment for relapse, assessments during retreatment will be grouped into Retreatment Period specially.

Table 2-1 Analysis Period for Data

Analysis Period	Start Time Point	End Time Point
Core Period	Day 1	For participant who won't join in Extension Period: Date of End of study visit; For participant who join in Extension Period: End of Core visit (Day 43)
Extension Period	For participant who join in Extension Period: Date of End of Core visit + 1	For participant who join in Extension Period: Date of End of Study visit
Retreatment Period	For participant who take retreatment: Date of first dose of retreatment	For participant who take retreatment: Date of last Retreatment visit

__Analysis visit and windows__

Since the actual visit for a participant may not exactly coincide with their targeted visit date, the actual visit date will be mapped to an analysis visit for the purpose of data summary and model analysis. However for assessments (except for PK sampling) performed at -2 hours, -1 hour, 20 min, 40 min, 2 hours, 4 hours on the same day, there is no need to remap visit time, so site collected timepoint will be analysed.

The visit window in Table 2-2 defines the analysis visit applicable for assessments in Core Period and Extension Period, including efficacy endpoints (e.g. MADRS, [redacted]), safety endpoints (e.g. laboratory, vital signs, ECG, [redacted]

Table 2-2 Analysis Visit Windows for Core Period and Extension Period

Analysis Period	Study Visit	Target Day/Time	Study Day
Core Period	Baseline	Day 1 -2 hours predose (See definition for baseline in Section 2.1.1)	-2, - 1, 1 (predose)
	D1 20 min, 40 min, 2 h, 4 h	Day 1 20 min, 40 min, 2 hours, 4 hours post dose	1 (post dose)
	24 h	2	2
	D8	8	3 - 11
	D15 -2 h, -1 h, 40 min, 2 h, 4 h	Day 15 -2 hours, -1 hour predose, 40 min, 2 hours, 4 hours post dose	12 - 18
	D22	22	19 - 25
	D29 -2 h, -1 h, 40 min, 2 h, 4 h	Day 29 -2 hours, -1 hour predose, 40 min, 2 hours, 4 hours post dose	26 - 32
	D36	36	33 - 39
	D43	43	40 – End of Core Visit
Extension Period	2 weeks follow-up	57	(End of Core Visit + 1) - 64
	4 weeks follow-up	71	65 - 85
	Monthly follow-up post Day 43	43 + (n)*28 *n is the nth month follow up*	(-13, +14) of target day *The last follow-up visit will last until the end of study*

The main analyses will summarize data collected in Core Period up to 2 weeks follow up in Extension Period. The monthly follow-up visit in Extension Period will not be presented in by-visit summary, unless otherwise specified.

In addition for participants who are retreated during Extension Period, assessments performed during Retreatment Period will be mapped to the analysis visit according to Table 2-3.

Table 2-3 Analysis Visit Windows for Retreatment Period

Analysis Period	Study visit	Target Day since start of retreatment*	Day since start of retreatment*
Retreatment Period	Baseline of Retreatment	Day 1 -2 hours pre-retreatment (See definition for	1

		baseline of retreatment in Section 2.1.1)	
	Retreatment D1 40 min, 2 h, 4 h	Day 1 40 min, 2 hours, 4 hours post retreatment	1
	Retreatment 24 h	2	2
	Retreatment D8	8	3 - 11
	Retreatment D15 -2 h, -1 h, 40 min, 2 h, 4 h	Day 15 -2 hours, -1 hour predose, 40 min, 2 hours, 4 hours post dose	12 - 18
	Retreatment D22	22	19 - 25
	Retreatment D29 -2 h, -1 h, 40 min, 2 h, 4 h	Day 29 -2 hours, -1 hour predose, 40 min, 2 hours, 4 hours post dose	26 - 32
	Retreatment D36	36	33 - 39
	Retreatment D43	43	40 – End of Retreatment Visit

* See the definition for Day(s) since start of retreatment in Section 2.1.1

When multipe assessments are mapped into the same window, following rules will be applied for efficacy and safety endpoints (except ECG) and PROs:

When assessments for scheduled visit and unscheduled visit are both present within the same window, the scheduled assessments value should be used. Unscheduled visit will only be used when there is no measurement from the scheduled visit in the defined window. Two special cases need to be handled as following rule:

- When assessments on a dosing day drop to the window of a non-dosing visit, for example the dosing on Day 15 was delayed to the window of Day 22, the pre-dose assessment will be mapped to the non-dosing visit of Day 22, while the post-dose assessment will not be mapped. Unless scheduled assessments for Day 22 were performed, the scheduled ones should be mapped then.
- When assessments on non-dosing day drop to the window of a dosing visit, for example the visit Day 8 was delayed to Day 15 and no dosing was administered, assessments will be mapped to the pre-dose hour of this dosing visit. Unless the dosing were administered and scheduled assessments performed within the window, the scheduled assessments should be mapped then.

In case of multiple assessment values among the same type of visit (i.e. two unscheduled assessments) within the same analysis window, the closest to the scheduled visit day will be used. In case of equal distances (e.g same day), the latest assessment value will be used. The exception is an assessment at early study withdrawal visits along with another assessment within a window. In such cases, the early-withdrawal assessment will be used.

For ECG, the same strategy will be applied except that no prioritization of scheduled vs unscheduled visit will be made.

2.1.3 Analysis sets

The Randomized Set (RAS) consists of all randomized participants. The descriptions of population will be based on RAS.

The Full Analysis Set (FAS) comprises all randomized participants who received at least one dose of randomized study treatment. Participants will be analyzed according to the treatment they have been assigned to during the randomization procedure. The primary efficacy analysis for data in Core Period will utilize this analysis set.

The Safety Set (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the treatment received. In case participants take the wrong treatment (different with the assigned treatment), the first treatment received will be used in analysis. Safety analysis for data in Core Period will be based on SAF.

The Extension Set (ENS) is defined to include all subjects who joined Extension Period. Data collected during follow-up period will be analyzed based on ENS, and grouped by the assigned treatment in Core Period. In case participants take the wrong treatment during Core, the first actual treatment taken will be used for the analysis of safety data only. The analysis of data collected during extension period (before and after re-treatment period) will be based on ENS.

The Retreatment Set (RTS) is defined as a subset of SAF including participants who received at least one dose for the retreatment of relapse. Participants will be analyzed according to the treatment received for the first injection during the Retreatment Period. The efficacy and safety endpoints pertinent to Retreatment Period (see Table 2-1) will be analyzed based on RTS.

PK Analysis Set (PKS) includes all participants who provided at least one evaluable PK concentration. Determined PK concentrations may be excluded from the PKS (per the scientific judgement of the PK scientist, e.g. non-plausible concentrations. All subjects within the PK analysis set will be included in the PK data analysis. PK samples from subjects treated with MIJ821 will be measured and PK samples from placebo treated subjects will not be measured.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.2 Patient disposition, demographics and other baseline characteristics

Demographic variables and other baseline characteristics will be summarized for each randomized treatment arm and for all participants based on RAS.

At baseline, the following demographic and baseline characteristics will be summarized:

- Age
- Weight and height
- BMI, and BMI group (<18.5, 18.5 to < 25, 25 to <30, 30 to < 40, >=40)
- Sex (Male vs Female)
- Ethnicity
- Race
- Disease duration (years): date of informed consent - date MDD first diagnosed in Major Depressive Disorder History
- Antidepressants at baseline (ongoing taken during study) in category of
    - Tricyclic Antidepressants (TCAs)
    - Selective Serotonin-Reuptake Inhibitors (SSRIs)
    - Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)
    - Other Antidepressants
- Total number of depressive episodes in history (excluding the current episode): 0, 1-2, 3-5, >5

- Overall severity of current episode (moderate, severity)
- Current major depressive episode features
- Number of hospitalization events for current episode and by category (1, 2, >2)
- Reason for discontinuation of prior MDD treatment failure
- Number of MDD treatment failures (due to lack of efficacy or adverse event), in category of (<2, ⩾ 2, unknown due to missing)
- Baseline MADRS score
- Baseline MADRS score in category of <30, 30-34, 35-40, >40

[redacted]

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables for each randomized treatment arm and for all participants (total) using RAS. The number and proportion of participants will be presented for categorical variables by treatment arm and all participants (total).

If multiple races have been reported for a participant, the participant will be categorized as multiple races and in each selected race category.

Demographics and baseline characteristics will be listed by treatment arm.

Relevant medical histories and current medical conditions at baseline will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment arm.

2.2.1 Patient disposition

Randomized

Participants are considered randomized if they have been assigned a randomization number.

Completing the Core Treatment

Participants are defined as completing the Core Treatment if they have received 3 scheduled infusions in Core Period. It will be derived from Treatment Disposition Form with "Completed" as participant status. Participant who has infusion interruption or skips the second infusion on Day 15 will not be counted as treatment discontinuation if she/he completes the last infusion on Day 29.

Completing the Core Period

Participants are defined as completing the Core Period if they completed the End of Core Visit (Day 43). Participants who discontinue core treatment are encouraged to continue the scheduled visit as indicated in the Assessment Schedule (Protocol Table 8-1).

Eligible for Retreatment in Extension Period

Participants who complete the Core Period on study treatment (with Day 29 infusion completed), and are classified as responders or remitters at the end of Core Period, will be eligible for retreatment with MIJ821 once observe relapse during the Extension Period.

Completing the Retreatment in Extension Period

Participants who are eligible for retreatment and have received 3 scheduled infusions in Extension Period, will be considered as completing the retreatment. It will be derived from Retreatment Disposition Form with "Completed" as participant status. Participant who has infusion interruption or skip the second infusion on Day 15 (Retreatment Period) will not be counted as treatment discontinuation if she/he completes the last infusion on Day 29 (Retreatment Period).

Completing the Extension Period

Participants who are classified as responders or remitters at the end of Core Period will be deemed as completing the Extension Period if they have been observed for 52 weeks in Extension Period or up to clinical worsening after re-treatment, whichever comes first. Participants who are neither responders nor remitters at end of Core Period will be deemed as completing the Extension Period if they have completed the minimum 8 weeks' safety follow-up in Extension Period.

Participant disposition will be displayed by randomized treatment and overall, in terms of:

- the number and proportion (based on the number of participants within each randomized treatment arm) of participants who receive Core Treatment, complete the Core treatment or discontinue the Core treatment prematurely along with the primary reason, based on RAS
- the number and proportion of participants who completed Core Period or discontinue the Core Period prematurely along with the primary reason, based on RAS
- the number and proportion of responder or remitter at End of Core Visit, as well as the number and proportion of non-responder and non-remitter at End of Core Visit, based on RAS
- the number and proportion of participants who completed the retreatment or discontinued the retreatment prematurely along with the primary reason, based on RTS
- the number and proportion of participants who completed the Extension Period or discontinue the Extension Period prematurely along with the primary reason, based on ENS

In addition, the total number of participants screened, rescreened and screen failed, including the reason for non-inclusion into the study will be provided, based on all screened subjects.

If participants discontinued from study prior to the scheduled visit at 24 hours, the primary efficacy assessment will not be available. Those cases will be flagged along with discontinuation reasons.

The break down of randomization population into each of the analysis sets (see Section 2.1.3) will be provided in summary table. The exclusion reason from each analysis sets will be listed (see exclusion rule in Appendix 5.2).

The number of participants with non-pandemic related PDs and pandemic related PDs according to the applicable SOP will be presented. The results of the PDs will be grouped using the broad categories defined in the applicable SOP. A complete list of the PDs can be found in the Edit Check Specifications document in CREDI. Participants with PDs and non-PDs leading to data exclusion from analysis sets will be listed.

2.3 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.3.1 Study treatment / compliance

Descriptive statistics will be produced to describe the exposure to investigational product by treatment arm based on SAF, in terms of:

- the number of participants who received 1, 2 or 3 injections in Core Period. In addition for MIJ821 dose group, the number of injections with active MIJ821 dose will be counted.
- total duration of exposure, calculated by (last injection date – first injection date + 14) days: (for MIJ821 single infusion + 2 subsequent placebo infusions, the last dose date will count placebo infusion as well).

For each visit, the number and proportion of participants receiving study drug will be summarized. The dose change and reason, the duration of each infusion as well as interruption/discontinuation reasons (if applicable) will be listed.

The similar analyses will be provided for retreatment based on Retreatment Set (RTS).

2.3.2 Prior, concomitant and post therapies

For the standardization of data display, concomitant medications 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 (ATC) system. Non-drug therapies or procedures will be coded by Medical Dictionary for Regulatory Activities (MedDRA). The data analysis in this section will be based on the coded terminology. Frequency summary (count and proportion) will be provided by ATC (1, 3, 4) and coded name for medications, and by system organ class (SOC) and preferred term (PT) for non-drug therapies.

The missing or incomplete start/stop date of medication/therapy will be imputed before data handling (see imputation rule in Appendix 5.1.2)

Standard of Care

Participants must receive pharmacological antidepressant therapy during study. Dosage titration or adjustments of SoC occurring within the first 2 weeks of Core Period are allowed, if needed, with dosages maintained thereafter during the Core period. The SoC includes antidepressant or augmentation, which will be identified by the category of "MDD Related Medications" from CRF form - "Concomitant medication" The SoC during Core Period will be summarized by ATC level (1, 3, 4) and preferred term.

The adjustment of SoC beyond the first 2 weeks potentially may lead to confounding effect to the efficacy assessments over 6 weeks in Core Period. So, any adjustment of SoC post the first 2 weeks will be flagged at individual participant level in listing and the impact on efficacy assessment will be indicated (e.g. adjustment of SoC beyond first 2 weeks in Core Period).

The adjustment of SoC will also not be allowed beyond the first 2 weeks of Retreatment Period. Any adjustments of SoC in Retreatment Period will be flagged similarly in listing but no summary will be provided.

Prohibited Medications and Therapies

The prohibited medications/therapies or those with potential confounding effect for efficacy will be flagged according to [redacted] The impact on efficacy assessments will be evaluated based on the start date/time of taking those prohibited medications/therapies and the protocol deviation report, indicating like “Taken prior to MADRS assessment at 24 hours” “Taken post 24 hours in Core Period” “Taken in Extension Period”. If data warranteed, prohibited medications/therapies taken prior to MADRS assessment at 24 hours will be summarized by ATC level (1, 3, 4) and PT for medications, and by SOC and PT for non-drug therapies, and present by listing.

[redacted]

Rescue Medications

The rescue medications could be given to treat agitation, anxiety or aggressive behaviour per investigator judgement or local clinical practice. The recommended rescue medication is 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).

The list of rescue medications taken by patient prior to MADRS assessment at 24 hours will be manually reviewed and confirmed via clinical review.

The rescue medication taken prior to MADRS assessment at 24 hours will be flagged in listing as they might have confounding effect to the primary endpoint.

Other Medications and Therapies

The prior MDD related medications and non-MDD related medications will be summarized ATC level (1, 3, 4) and PT.

The prior MDD related non-drug therapies and non-MDD related non-drug therapies including psychotherapy will be presented in listing.

The concomitant MDD related non-drug therapies, and non-MDD related non-drug therapies will be summarized by SOC and PT separately for Core Period and Retreatment Period.

Other non-MDD related concomitant medications will be summarized by ATC level (1, 3, 4) and PT.

2.4 Analysis of the primary objective

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 patients with MDD who have suicidal ideation with intent, while accounting for intercurrent events with potential confounding effects and intercurrent events leading to study discontinuation prior to the 24 hours assessment.

2.4.1 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 with potential confounding effects and intercurrent events leading to study discontinuation prior to the 24 hours assessment.

Population: Participants with MDD who have suicidal ideation with intent. All participants included in FAS will be counted.

Variable: Change from baseline in MADRS total score at 24 hours post first dose administration (see definition in Section 2.4.1.1)

Treatment:

There are 6 active MIJ821 dose arms and 1 placebo arm as described in Section 1.1.

- 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

Since the MADRS total score at 24 hours will be evaluated post the single first injection, treatment arms with different regimens will be grouped into one arm, which turns out to be 4 pooled dose arms and 1 placebo arm during the analysis of this primary estimand:

- Placebo every other week
- MIJ821 0.0048 mg/kg
- MIJ821 0.016 mg/kg
- MIJ821 0.048 mg/kg
- MIJ821 0.16 mg/kg

on 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 (not limited to):

Intercurrent events with potential confounding effect to MADRS assessment at 24-hour:

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

Participants who took prohibited medications/prohibited therapy treatment or concomitant medications with potential confounding effect and rescue medications will continue to stay in the study. The confounding effect from these medications or therapies will be identified by the approach defined in Section 2.3.2.

Intercurrent events leading to study discontinuation prior to the 24 hour assessment:

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

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

2.4.1.1 Primary endpoint

The primary endpoint is the change in MADRS total score from Baseline (Day 1, predose) to 24 hours post first dose in the Core Period. The baseline assessment and the subsequent assessments during study use a 7-day recall period, except that the assessments at 4 hours post dose on dosing day uses a 4-hour recall period, and the assessment at 24 hours post first dose uses a since-last-evaluation recall period.

The MADRS consists of 10 items that cover all of the core depressive symptoms (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts). For the MADRS performed at 4 hours post dose on Day 1, Day 15 and 25, the MADRS scores for the sleep item and appetite are not recorded and the recorded predose value within the same day will be carried forward. Each item is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptom). A total score (0 to 60) is calculated by adding the scores of all 10 items. For each item as well as the total score, a higher score represents a more severe condition.

If 2 or more items are missing, no imputation will be performed and the total score will be left missing. Otherwise, the total score will be calculated as the sum of the items present multiplied by the ratio of the maximum possible number of items (i.e., 10) to the number of items present:

Total score = Sum of scores from items present*(10/number of items present)

[redacted]

[redacted]

[redacted]

2.4.4 Handling of missing values/censoring/discontinuations not related to intercurrent event

For other missing cases which are not caused by intercurrent events defined in [redacted], data will be imputed using a MAR mechanism for all treatment arms.

[redacted]

[redacted]

2.4.6 Supportive analyses

MADRS score over visit

Based on FAS, the summary statistics for absolute values and change from baseline of MADRS score by treatment arm (6 dose arms and 1 placebo arm) and analysis visit in Core Period and 2 weeks follow-up in Extension Period, will be provided for the original measurements (i.e. the raw data prior to missing data handling using multiple imputation) of the primary endpoint.

The change from baseline in MADRS score (original measurements) from above visits will also be analyzed using the mixed-effects model for repeated measures (MMRM). This model will include the fixed, categorical effects of treatment, region, time (all analysis visits), and treatment*time interaction, as well as the continuous, fixed covariates of baseline MADRS score, and baseline MADRS score*time interaction. An unstructured variance-covariance structure will be used to model the within-subject errors. The Kenward-Roger method will be used to adjust the estimated covariance of the mean difference and the degrees of freedom. If the analysis with unstructured covariance structure fails to converge, the compound symmetry will be tested. Model estimated means and their differences of each MIJ821 doses vs. placebo, will be obtained at each timepoint, along with the 90% CI for the difference. Model estimated treatment means in change from baseline in MADRS score (±SE) will be plotted over time/visit.

For participants who take retreatment for relapse, the summary statistics for absolute values of MADRS score and change from the baseline of retreatment will be provided in the similar manner, based on RTS. No inferential test analyses will be performed for the retreatment due to limited data.

The individual MADRS scores will be presented in listing.

Individual Item Analyses

Descriptive statistics (n, median, minimum and maximum) will be provided for MADRS item 10 ("Suicidal thoughts") score at baseline and the changes from baseline value at each visit. The treatment difference will be estimated for item 10 using the Hodges-Lehmann estimate, which is the median of all possible paired differences for the change from baseline for individual item. Hodges-Lehmann estimates and the corresponding 90% CI for the treatment differences will be provided for each timepoint.

[redacted]

2.5 Analysis of secondary efficacy objective(s)

There will be no estimand defined for secondary objective(s) in this analysis plan. [redacted].

2.5.1 Secondary endpoints

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.
  - Participants who do not meet the criterion or discontinue Core Period prior to the time point due to any reason or with missing score (baseline and/or post baseline) will not be considered as "a responder" at that timepoint.
- 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

- The sustained response ideally requires all scheduled assessments over four weeks achieving 50% reduction from baseline. However, if there is one or more missing assessment(s) between two responses, the response will be assumed to be sustained over missing assessment(s), unless other specified. For example, one participant observed a response at Day 1 4 hours, Day 29 -2 hours, however missed the assessment at 24 hours, Day 8, Day 15 and Day 22, this participant is still considered as meeting the sustained response. The missing due to study discontinuation will not be imputed. Participants who do not meet the criterion will not be considered as "a responder" at the timepoint.

- Proportion of participants meeting remission criteria (MADRS total score of ≤12) over time in Core Period
  - Participants who do not meet the criterion or discontinue prior to the time point due to any reason or with missing score (either at baseline or post baseline) will not be considered as "a remitter" at that timepoint.
- 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
  - The rule for sustained remission is the similar with sustained response. Participants who do not meet the criterion will not be considered as "a remitter" at the timepoint.
- Proportion of participants meeting criteria for relapse over fixed period in the Extension Period
  - The definition and criteria of relapse could be referred to protocol section 3.4. The relapse will be evaluated by investigator and reported in the CRF form "Relapse and re-treatment criteria". Participants without relapse reported will not be counted.
- Proportion of relapsing participants meeting response criteria or remission criteria after the first infusion of MIJ821 retreatment in the Extension Period
  - After the retreatment, the proportion of participants meeting response or remission criteria again will be derived based on all relapsing participants who have achieved response or remission at the end of Core Period.

2.5.2 Statistical hypothesis, model, and method of analysis

Analysis of above secondary efficacy endpoints will be based on FAS (Core Period) or RTS (Retreatment Period), except the following endpoints:

- Proportion of participants meeting criteria for relapse over fixed period in the Extension Period will be based on ENS
- Proportion of relapsing participants meeting response criteria or remission criteria after the first infusion of MIJ821 retreatment in the Extension Period will be based on RTS

No hypothesis will be tested for the secondary efficacy endpoints.

Frequency tables (count and proportion) will be provided for these endpoints by analysis visitafter imputation for missing values. Details on missing data handling are described in Section 2.5.1. Bar chart will be plotted by treatment arm and analysis visit.

The proportion of participants meeting criteria for relapse over 1 month, 2 months, 3 months, 6 months 9 months and 12 months in Extension Period will be plotted for each treatment arm based on ENS for responders/remitters at EoC visit. In addition for responders/remitters, the time to first relapse will be analyzed by kaplan-meier (KM) method and display in KM plots. The median time to first relapse will be summarized with 90% CI.

If data warranted, the treatment differences of each MIJ821 dose versus Placebo will be analyzed separately, using a repeated logistic regression model, for following endpoints:

- 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

For response rate and remission rate per visit, the repeated logistic regression model will be established with the fixed, categorical effects of treatment (6 dose arms and 1 placebo arm), time, treatment*time interaction, region, the fixed continuous baseline MADRS score, and baseline score*time interaction. [redacted]

For sustained reponse rate and remission rate, the logistic regression model with firth method will be fitted, involving fixed, categorical effects of treatment (6 dose arms and 1 placebo arm), region, and the fixed continuous baseline MADRS score. The estimated arm-level effect, treatment difference and the corresponding 90% CI will be obtained by applying the same standardization procedure as above.

The response or remission at each assessment will be flagged out in the individual listing of MADRS scores.

2.5.3 Handling of missing values/censoring/discontinuations

The handling of missing data has been described for each endpoint in Section 2.5.1. The missing value due to discontinuation will not be imputed.

2.6 Safety analyses

The safety and tolerability of MIJ821 will be evaluated by adverse events, clinical significant findings from laboratory test, physical examination, vital signs, 12-lead ECG, holter ECG and safety scales.

Unless otherwise stated, the safety data listed in following subsections will be analyzed separately for Core Period based on SAF and Retreatment Period based on RTS. For the summary of change from baseline in Retreatment Period, the baseline will be the last valid assessment before retreatment, i.e. the baseline of retreatment.

2.6.1 Adverse events (AEs)

Treatment-Emergent Adverse Events (TEAEs) are defined as adverse events starting or worsening after the first dose of study medication and 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 missing onset date of AE will be imputed before identify the TEAE (see imputation rule in Appendix 5.1.1)

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later will be used to code Adverse Event (AE) to a SOC and a PT.

TEAEs will be analyzed separately for Core Period and Retreatment Period:

- The summary of TEAEs in Core Period (up to 2 weeks post the last dose) will be based on SAF
- The summary of TEAEs in Retreatment Period (up to 2 weeks post the last dose of retreatment) will be based on RTS

The number (and percentage) of participants with TEAEs will be summarized by following approach as defined in Table 2-7, in terms of all TEAEs, Treatment-Emergent Serious Adverse Events (TESAEs), TEAEs leading to treatment discontinuation, treatment-related TEAEs or TESAEs and death:

- 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
- by treatment, preferred term with most frequent (incidence rate ≥ 5%)

Table 2-7 AE Summaries of Subject Incidence

Category	by SOC and PT	by SOC, PT and maximum severity	by most frequent PT (≥ 5%)
All TEAEs	Y	Y	Y
TESAEs	Y		
AEs leading to treatment discontinuation	Y		
Treatment-related TEAEs	Y		
Treatment-related SAEs	Y		
Deaths	Y		

For all AEs tables presented by SOC and PT (and grade), the SOCs will be presented in alphabetical order and PTs will be ordered within the SOC by decreasing order of frequency. AE tables by preferred term only will be sorted in descending order of frequency.

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.

[redacted]

All AEs, deaths, SAEs and AEs leading to permanent study drug discontinuation will be listed separately.

For clinical trial safety disclosure to ClinTrials.gov (CT.GOV) and European Union Drug Regulating Authorities Clinical Trials (EudraCT) at end of study, following summaries will be provided.

Table 2-8 Clinical Trial Safety Disclosure Requirements

	Requirements	CT.GOV	EudraCT
SAE	Number of subjects who had treatment emergent / on-treatment SAE	Y	Y
	Number of subjects who had on-treatment death	Y	Y
	Number of subjects who had on-treatment death due to SAE that were causally related to treatment		Y
	Number of SAEs by SOC/PT	Y	Y

	Number of occurrences of SAEs by SOC/PT		Y
	Number of occurrences of SAEs that were causally related to treatment by SOC/PT		Y
	Number of SAEs, with outcome of death, related to treatment/all by SOC/PT		Y
NSAE	Number of subjects who had treatment emergent / on-treatment Non-SAE(NSAE) with 0-5% threshold	Y	Y
	Number of NSAEs (0-5% threshold) by SOC/PT	Y	Y
	Number of occurrences of NSAE with 0-5% threshold by SOC/PT		Y

2.6.1.1 Adverse events of special interest / grouping of AEs

Based on the current available information, 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. MedDRA search criteria for AESIs will be identified by the latest version of electronic Compound Case Retrieval Strategy (CRS).

- 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

AESI will be summarized by risk name and PT respectively for Core Period and Retreatment Period. The time to onset on each doing day, starting from first dosing, starting from the most recent dosingand time to resolution (starting from first onset date) of each AESI at risk level will be summarized by descriptive statistics. For multiple AESIs per subject, the earliest onset time and the latest resolution time will be counted per subject. For AESI occurred on dosing day, a listing will be provided with the time to onset (starting from first dosing, starting from the most recent dosing) and time to resolution (starting from onset date) by risk name and PT term for each participant. AESIs occurred on non-dosing days will be presented by listing in similar manner.

In addition, the by AESI category as listed above and by PT summary will be provided for AESI identified by investigator and reported in CRF AE form under the Adverse Event Category of "Adverse event of special interest". A listing will be provided as well.

2.6.2 Deaths

Deaths will be listed by actual treatment arm including the start date of the study treatment, the last dose date on study treatment, the death date and the primary cause (and contributing cause if any) for death.

2.6.3 Laboratory data

For Core Period up to 2 weeks' follow up visit, and seperately for the Retreatment Period, following analyses will be provided for laboratory data by treatment arm and analysis visit:

- Average change from baseline of laboratory hematology, blood chemistry results in forms of table.
- The number and proportion of participants with newly occurring or worsening clinical abnormality (outside normal range). For newly occurring event, the participant needs to have a baseline value that is not clinically abnormal for that parameter. For participant with missing baseline value, any post-baseline abnormal value will be considered as newly occurring. For worsening event, the participant needs to have a baseline value that is clinical abnormal and also have a worse post-baseline value.
- Listing of participants with abnormal laboratory values.

To evaluate the potential drug-induced hepatotoxicity and renal signal, the liver and renal abnormalities will be analyzed by:

- the number and proportion of participants with any liver enzyme abnormalities based on each criteria defined in Table 5-3 in Appendix.
- the number and proportion of participants with any renal abnormalities based on each criteria defined in Table 5-4 in Appendix.
- listings of participants with clinically liver or renal abnormality.

2.6.4 Other safety data

2.6.4.1 ECG and cardiac imaging data

The average triplicate values of 12-lead ECG results and the change in these results from the most recent dose will be summarized for each visit. The absolute value of QTcF will be ploted by box and whisker plot. The incidence of abnormal ECG (see Table 5-5 in appendix) will be presented by treatment arm and by analysis visit and also in listing. The ECG finding will only be presented in listing.

Ambulatory Holter ECG will be recorded for 25 hours for all participants at randomization Day 1 for 25 hours, starting at least 1 hour before the start of the first infusion. Two kinds of device, Holter GI (Global Instrumentation) and Holter patch, will be used in different regions respectivly. The abnormality findings from Holter for individual participant will be provided by lisiting, with the information of the date of first dose, the device type (GI or patch).

2.6.4.2 Vital signs

The change from baseline of vital signs (systolic/diastolic blood pressure, pulse rate, temperature) and weight will be summarized by treatment arm and by analysis visit, for Core Period up to 2 weeks' follow up visit, and seperately for the Retreatment Period.

In addition, for systolic/diastolic blood pressure, the change from most recent dose will be summarized in a similar manner.

For Core Period up to 2 weeks follow up visit, the mean (SD) of change from baseline will be displayed by line plot. The change from the each dose up to 2 weeks will be plot in the same manner.

The proportion of any clinical relevant abnormality postbaseline and break donw by visit will be summarized and presented in listing at individual level.

[redacted]

[redacted]

[redacted]

2.6.4.6 Others

In case of cystitis or other lower urinary tract event, the PRO Bladder Pain/Interstitial Cystitis Symptom Score will be assessed. The PRO results will be presented in a listing.

The memory assessment will be performed to evaluate the present and absent of memory gap/amnesia using orientation questions. The individual assessment results will be presented.

2.7 PK analyses

Variables

The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8.0 or higher):

- Following first infusion in Core Period:
    - AUClast, Cmax, and Tmax will be determined from the plasma concentration-time data.
    - If data allow, secondary PK parameters will be estimated like T1/2, AUC0-t (t represent the end of the observation period of interest), AUCinf, CL, Vz (list of parameters are not limited).
- Following all other infusions in Core Period and all infusions in Relapse Retreatment Period:
    - PK samples will be collected at pre-dose (if scheduled), 40 min (end of infusion), and 4 h after end of infusion. The PK sample at the end of infusion (40 min) represents the Cmax and Tmax values. No other PK parameters will be estimated.

Descriptive analyses

All MIJ821 plasma concentrations and PK parameters including their descriptive statistics will be presented with three significant figures for Core Period and Relapse Retreatment Period. The exception will be %CV (Coefficient of Variation) values, which will be reported to one decimal place and N values, which will be reported as whole integers.

For the summary statistics of plasma concentration, the following time windows are defined: predose:

Table 2-11 Time window for plasma concentration

Nominal time after start of infusion	Elapsed time after start of infusion
0	All times before start of infusion
20 min	20 min +/- 2 min
40 min	40 min +/- 2 min
4 hours	4 hours +/- 30 min
24 hours	24 hours +/- 1 hour

Concentrations collected outside of the time windows will be not used for summary statistics of plasma concentrations. The time windows will be used for all infusions. For the PK parameter estimation, all concentrations with a recorded elapsed time will be used.

Summary statistics of plasma concentrations and PK parameters will be provided on separate tables and will include: mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum, N value, by dose(/regimen) and study period. Concentrations below LLOQ (Lower Limit of Quantification) 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. An exception to this is Tmax where median, minimum and maximum will be presented.

MIJ821 plasma concentrations will be expressed in mass per volume. Concentrations below the LLOQ will be reported as zero.

The plasma concentrations will be listed by

- study period, regimen, dose, subject, and visit/sampling time point

Overall descriptive summary statistics of plasma concentrations will be provided by

- study period, regimen, dose, and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ, and
- study period, dose and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ

PK parameters of each subject will be listed separately for the two dose regimens (one listing for repeated dosing, one listing for single dose) across Core and Retreatment dosing periods by:

- subject, dose, [redacted] visit

Overall descriptive summary statistics of PK parameters following the first infusion in Core Period will be presented by:

- regimen, dose
- dose (combined dose regimens)

Overall descriptive summary statistics of PK parameters following all other infusions in Core Period and all infusions in Relapse Retreatment Period will be presented by:

- study period, regimen, dose, and visit/sampling time point

Graphs

The following concentration-courses of MIJ821 in plasma will be generated:

- Summary plot – Core part (linear and semi-logarithmic view)
  Arithmetic mean (SD) plasma concentration-time course per dose after first infusion across both dose regimens (overlaying)

- Summary plot – Core part (linear and semi-logarithmic view)
  Plasma concentration-time course per dose after first infusion across both dose regimens (spaghetti plot, individually per dose)
- Summary plot – Core part (linear and semi-logarithmic view)
  Arithmetic mean (SD) plasma concentration-time course per dose and per dose regimen after first infusion (individually per dose)
- Summary plot – Core part (linear and semi-logarithmic view)
  Plasma concentration-time course per dose and per dose regimen after first infusion (spaghetti plot, individually per dose)
- Summary plot – Core part (linear and semi-logarithmic view)
  Arithmetic mean (SD) plasma concentration-time course per dose and dose regimens across all infusions (overlaying)
- Summary plot – Retreatment (linear and semi-logarithmic view)
  Arithmetic mean (SD) plasma concentration-time course per dose and dose regimen across all infusions (overlaying)
- Individual plot (linear)
  Plasma concentration-time course per individual across all infusions in Core and Retreatment study part

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.11 Interim analysis

One unblinded analysis will be performed when all participants completed Day 57 (2 weeks follow-up visit after the End of Core visit on Day 43). Data from Core Period will be analyzed according to the plan herein. The optimal dose will be identified based on the dose-response relationship established by MCP-Mod, as well the sustained efficacy effect, safety profile and PK of each MIJ821 dose and regimen compared to placebo.

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

3 Sample size calculation

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 2.4.2. [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 patients. 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 arms) 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.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

Missing or incomplete dates will be listed as it is in any listings.

Incomplete or missing start date and end date of an adverse event will be imputed according to Novartis standards (details will be given in programming datasets specifications (PDS) document).

5.1.2 Concomitant medication/therapy date imputation

Incomplete or missing start date and end date of concomitant mediation records will be imputed according to Novartis standards (details will be given in programming datasets specifications (PDS) document).

[redacted]

[redacted]

5.2 Rule of exclusion criteria of analysis sets

Table 5-2 Subject Classification

Analysis Set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
FAS	NA	Not randomized No double-blind study drug taken
SAF	NA	No double-blind study drug taken
ENS	NA	Not enter into extension phase
RTS	NA	No retreatment administered No relapse observed None of responder or remitter
PKS	NA	Input from PK scientist

5.3 Abnormality criteria for laboratory, ECG and vital sign

Table 5-3 Liver Abnormality Criteria

Liver events defined by laboratory parameter abnormalities (additional non-lab criteria as provided in the protocol are ignored):

Parameter	Criterion
For each assessment:	ALT > 3x ULN ALT > 5x ULN ALT > 8x ULN ALT > 10x ULN ALT > 20x ULN ALT or AST > 3x ULN ALT or AST > 5x ULN ALT or AST > 8x ULN ALT or AST > 10x ULN ALT or AST > 20x ULN ALT or AST > 3x ULN & TBL > 1.5x ULN ALT or AST > 3x ULN & TBL > 2x ULN ALP > 1.5x ULN

Parameter	Criterion
	ALP > 2x ULN ALP > 3x ULN ALP > 5x ULN TBL > 1x ULN TBL > 1.5x ULN TBL > 2x ULN TBL > 3x ULN ALP > 3x ULN & TBL > 2x ULN ALP > 5x ULN & TBL > 2x ULN 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 and ALP ≤ 2 × ULN) Any clinical event of jaundice (or equivalent term)
If ALT or AST abnormal at baseline:	ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)

Table 5-4 Renal Abnormality Criteria

Criterion
• Serum creatinine increase 25 - <50% compared to baseline • Serum creatinine increase ≥ 50% compared to baseline • New dipstick proteinuria ≥3+ • New dipstick hematuria ≥3+ • Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)*

*Creatinine is not tested in urine according to protocol so urine PCR is not available in central lab data.

Table 5-5 ECG Abnormality Criteria

ECG Parameter	Abnormality Flags	
	Absolute	Relative*

RR Interval	Low: < 600 msec ; High: > 1200 msec	Low: ≤ -20%; High: ≥ 20%
PR interval	Low: < 120 msec ; High: > 200 msec	Low: ≤ -20%; High: ≥ 20%
QRS Interval	Low: < 60 msec ; High: > 109 msec; High: > 120 msec	Low: ≤ -20%; High: ≥ 20%; High: ≥ 25%
QT Interval	Low: < 320 msec ; High: >= 450 msec for male, >=460 for female; >500 for both	>30 to <=60 msec, >60 msec
QTcF Interval (Fridericia's correction)	Low: < 320 msec ; High: >= 450 msec for male, >=460 for female; >500 for both	>30 to <=60 msec, >60 msec
*Relative change from previous pre-dosing measurement in percent (%) for RR, PR, QRS, relative change in values compared with previous pre-dosing measurement in millisecond (msec) for QTcF Interval and QT intervals.		

Table 5-6 Vital Signs Abnormality Criteria

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	≥ 200 mg Hg > 180 mm Hg < 90 mm Hg	increase of ≥ 20 mm Hg increase of ≥ 40 mm Hg decrease of ≥ 20 mm Hg
Diastolic blood pressure	≥ 120 mg Hg > 105 mm Hg < 50 mm Hg	increase of ≥ 15 mm Hg increase of ≥ 25 mm Hg decrease of ≥ 15 mm Hg
Weight	Baseline weight (kg)	increase of ≥ 7% decrease of ≥ 7%

*bpm= beats per minute

6 Reference

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