NOVARTIS

Clinical Development

MIJ821

CMIJ821B12201 / NCT05454410

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

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Amendment v01
Release date:	16-Jan-2024
Number of pages:	47

Template Version 4.0, Effective from 23-Apr-2021

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
16-Jan-2024	Prior to DB lock	Amendment 01 version	[redacted]	
			Defined analysis window of ECG; In case of multiple records in the same window, no prioritization will be made for scheduled and unscheduled visits.	Section 2.1.2
			FAS will be analyzed based on assigned arms.	Section 2.2
			Subgroup variables updated	Section 2.2.1
			New baseline characteristics added, and some characteristics had categories adjusted. Baseline AD class data source changed from IRT reported to eCRF reported.	Section 2.3.2
			Imputation rule defined for MDE start date	Section 2.3.3
			Added rules for unblinded patient handling	Section 2.4.1
			MAOIs added as prohibited medication	Section 2.4.2.2
			Endpoint related to patient discontinued study or need new treatment was dropped since the information was covered in disposition and IE listings.	Section 2.6.1.1
			The term TEAE was changed to AE for simplicity AE summary by SMQ not applicable and deleted Separate summary of death/ fatal AE was removed since those was covered by SAE outputs AESIs were summarized separately on dosing day and overall	Section 2.7.1
			Updated summary for newly occurring and worsening lab parameters	Section 2.7.3 and Section 5.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Removed detailed CTCAE grade table in the Appendix since the standard macro will be applied	
			Boxplot for change from baseline in Component scores of CADSS was dropped and values were listed instead.	Section 2.7.4.3
			Sankey plots changed to stacked bar chart	Section 2.7.4.4 and Section 2.12
			C-SSRS summary changed to use standard table and listing	Section 2.7.4.5
			Details added for dose proportionalities	Section 2.8.3
			AE/CM imputation rules were deleted and were covered in PDS.	Section 5.1
			[redacted]	[redacted]
19-Aug-2022	Prior to DB lock	Creation of final version	First version	NA

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical classification
CADSS	Clinician-Administered Dissociative States Scale
[redacted]	[redacted]
[redacted]	[redacted]
CRF	Case Report Form
CRS	Case Retrieval Strategy
CS	Compound Symmetry
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT.GOV	ClinicalTrials.gov
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DMS	Document Management System
DR	Dose Response
[redacted]	[redacted]
[redacted]	[redacted]
EOS	End of Study
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FWER	Family-wise Error Rate
IA	Interim Analyses
IE	Intercurrent Events
IRT	Interactive Response Technology
[redacted]	[redacted]
LoE	Lack of efficacy
LS-means	Least Squares Means
[redacted]	[redacted]
MADRS	Montgomery Asberg Depression Rating Scale
MAR	Missing at Random
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MI	Multiple Imputation
MMRM	Mixed-effects Model for Repeated Measures
MNAR	Missing Not at Random
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
PD	Protocol Deviations
PDS	Programming Dataset Specification

[redacted]	
PK	Pharmacokinetics
PPS	Per-Protocol Set
[redacted]	[redacted]
PT	Preferred Term
RAP	Reporting & Analysis Process
s.c.	subcutaneous
SAE	Serious Adverse Events
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SNRI	Serotonin–Norepinephrine Reuptake Inhibitor
SoC	Standard of Care
SOC	System Organ Class
SSRI	Selective Serotonin Reuptake Inhibitor
TEAE	Treatment-emergent Adverse Events
TFLs	Tables, Figures, Listings
TRD	Treatment Resistant Depression
WHO	World Health Organization

1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analysis described in [Section 12] of the Protocol v02 (release date: 04-Nov-2022) for study CMIJ821B12201.

This SAP includes the detailed plans for the primary, secondary [redacted] objectives of the study as well as supplementary analyses for the primary objective and associated sensitivity analyses. All the statistical analysis results based on this SAP will be reported in the final Clinical Study Report (CSR). The analysis mentioned in this SAP will be performed by Novartis internal statisticians and programmers, if not specified differently.

[redacted]

1.1 Study design

This is a Phase IIa non-confirmatory, randomized, double-blind, placebo-controlled, parallel-group trial in participants with Treatment-Resistant Depression (TRD) to evaluate the efficacy, safety, tolerability, and pharmacokinetics of subcutaneous (s.c.) MIJ821 administration in addition to pharmacological antidepressant standard of care (SoC) treatment. The study design is illustrated in Figure 1-1.

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

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

The screening period starts when the participant signs the informed consent form and can last up to 28 days. The eligibility of participants is determined based on the assessments performed during the screening period and also on Day 1 (baseline/ prior to randomization).

Approximately 56 participants will be randomized to one of the above treatment arms via Interactive Response Technology (IRT) on Day 1/pre-dose in a blinded manner. The randomization will be stratified by the class of baseline anti-depressant SoC, which includes three categories: i) Selective Norepinephrine Reuptake Inhibitors (SNRI); ii) Selective Serotonin Reuptake Inhibitors (SSRI) and iii) other anti-depressants or any combinations.

In all treatment arms, the investigational treatment (MIJ821 or Placebo) is administered as a single s.c. injection on Day 1, followed by a safety observation at the clinical site for a minimum of 4 hours after administration. Details of the safety assessments and release criteria can be found in the protocol.

The post-dose follow-up period will continue for 4 weeks (28 days) after treatment. On-site visits to assess efficacy and safety are scheduled on Day 2 (24 hours post-dose) and

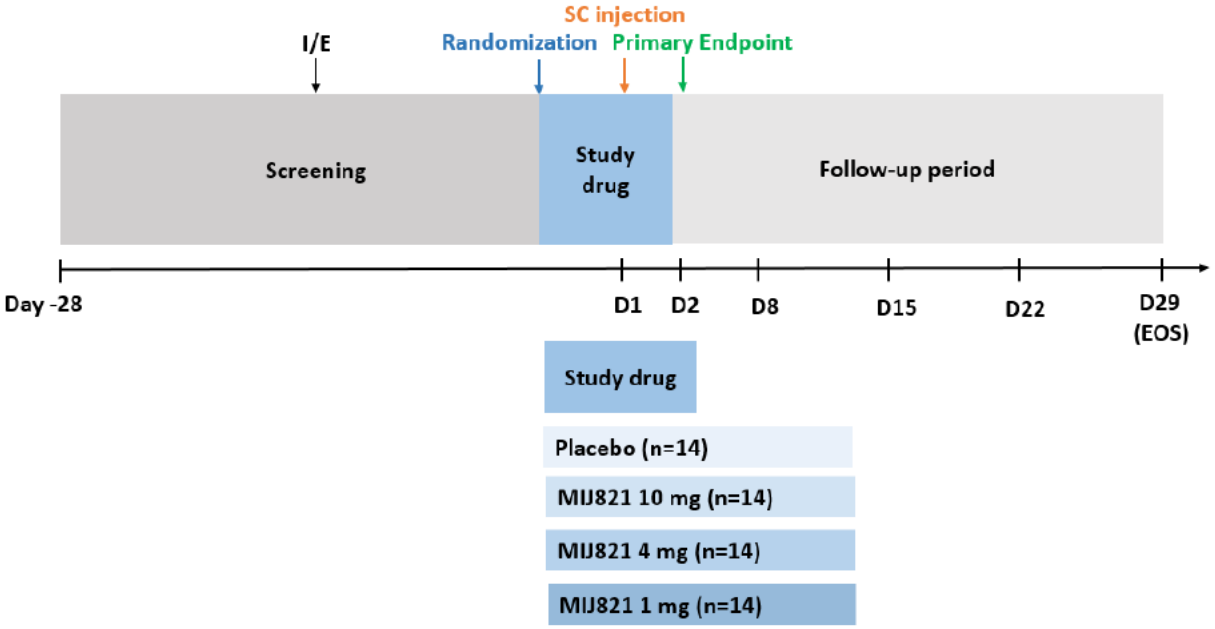
subsequently every week (i.e., on Days 8, 15, 22 and 29) during the follow-up period. The assessment to address the primary objective will be performed at Day 2 (24 hours post-dose). End-of-study (EOS) visit will be completed on site on Day 29. Phone calls will be conducted 3 days after each on-site visit (except for the EOS visit) to collect safety data including any AEs and concomitant medication use. The total duration of the study is approximately 8 weeks (56 days), including screening.

[redacted]

Safety monitoring will be conducted during the study using an independent Data Monitoring Committee (DMC). The analysis plan for DMC analysis will be covered in a different SAP.

All analysis covered in this SAP will be completed after the final database lock (DBL).

Figure 1-1 Study design



1.2 Study objectives, endpoints and estimands

Study objectives and related endpoints are described in Table 1-1 below. More details about the primary estimands are discussed in Section 1.2.1.

Table 1-1 Study objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess efficacy of MIJ821 (versus placebo) in treatment resistant depression after single s.c. injection	• MADRS total score at 24 hours after s.c. injection compared to baseline assessment

Objective(s)	Endpoint(s)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To assess safety and tolerability of MIJ821 after single s.c. injection	● Incidence and severity of treatment-emergent adverse events (TEAEs), including AEs of special interest; standard safety assessments such as vital signs, ECG, hematology, blood chemistry, urinalysis; Clinician-Administered Dissociative States Scale (CADSS) score, Modified Observer's Assessment of Alertness/Sedation (MOAA/S), C-SSRS, memory assessment using orientation questions, results of local tolerability assessments
● To assess MIJ821 PK in plasma after single s.c. injection	● PK properties of MIJ821 in plasma described by Area under the curve from time zero to time of last measurable concentration (AUClast), maximum plasma drug concentration (Cmax), time to reach maximum plasma concentration (Tmax) (parameters not limited).
● To assess the duration of antidepressant effect of MIJ821	● MADRS total score at Day 8, 15, 22 and 29 visits compared to baseline
● To characterize the dose-response and exposure-response relationship of MIJ821	● Dose-response relationship of MIJ821 with respect to change from baseline in MADRS total score at 24 hours after single s.c. injection ● Exposure-response relationship of MIJ821 with respect to change from baseline in MADRS total score at 24 hours (Day 2)

1.2.1 Primary estimand(s)

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

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

The primary estimand is described by the following attributes:

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

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

[redacted]

2 Statistical methods

2.1 Data analysis general information

Unless otherwise specified, the analysis results based on this SAP will be reported in the final CSR. The full scope of analysis will be performed by Novartis.

Analysis pertaining to Data Monitoring Committee (DMC) activities will be covered in a separate SAP.

Statistical analysis will be performed using SAS® statistical software (SAS Institute, Cary, NC, USA.) version 9.4 or later, and R version 4.1.0 or above.

Unless otherwise specified, summary tables/listings/figures will be presented for each treatment arm in the respective analysis set. In general, data of interest will be listed by treatment arm and by country/center number/subject id (/period/visit wherever applicable).

In general, assessments at scheduled visits will be analyzed (unless specified otherwise) and presented in Tables and Figures after visit remapping using analysis windows defined in Section 2.1.2. The assessment schedule is defined in protocol [Table 8-1], thus will not be repeated in this SAP. Listings will include both scheduled and unscheduled visits.

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. For selected parameters, 25th and 75th percentiles may also be presented. P-values will be presented only if a formal hypothesis test is performed.

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

2.1.1.1 Terminology – study drug

Study drug (treatment)

The study drug or study treatment refers to the medication MIJ821 or Placebo.

Standard of care (SoC)

Patients are expected to receive pharmacological antidepressant SoC treatment starting before screening. The class of the dominant antidepressant drug (SNRI, SSRI and other anti-depressants or any combinations) will be judged by physicians at baseline and used as stratification factor during randomization. The drugs and dosages used in SoC should be maintained during the entire study. Any change in SoC during the study must be documented in eCRF concomitant medication page with detailed date, time and indication. To be accurate,

the actual class of baseline antidepressants, which is based on the reported medications in the eCRF concomitant medication page, will be used in all the summary and analysis unless otherwise specified.

2.1.1.2 Study days and baseline derivation

Day 1

Day 1 or reference start date is defined as the day of dose administration (s.c. injection of the study drug). For participants who are randomized but not dosed, the Day 1 refers to the date of randomization.

Study day

The study day of a specific date of interest is calculated relative to Day 1 as follows:

Before Day 1: Study day = (Date of interest – Date of Day 1).

On or after Day 1: Study day = (Date of interest – Date of Day 1) + 1.

Note that there is no Day 0, the day before Day 1 is referred as Day -1.

Duration of an event is calculated as (event end date – event start date) + 1.

Baseline

Ideally the baseline values should be assessed at 1 hour before treatment on Day 1. In the analysis, a baseline value is defined as the last evaluable measurement prior to the study drug injection, irrespective of re-screening. In this case, baseline values will be the values obtained as the last valid pre-dose assessment on Day 1. If there is no valid assessment on Day 1, an earlier visit (scheduled or unscheduled) closest to the Day 1 visit will be picked and the last valid assessment on that day will be considered as baseline.

The actual assessment time (if available) should be used when comparing multiple records on the same day. If actual time is not available, the planned time point should be used. If neither applies, the last valid record (i.e. the one with the largest record number) will be used. More programming details will be provided in the Programming Data Specification (PDS).

Date of last contact

For participants who die during the study, the death date will be used as the date of last contact. For other participants, the date of last contact will be derived as the last visit assessment date.

Analysis cut-off date

All available data will be used. Data after withdrawal of consent will be excluded from all TFL outputs.

Treatment-emergent data

The treatment-emergent data is defined as data collected after the study drug injection on Day 1. Considering the short follow-up duration (29 days after baseline) of this study, all safety data

after study treatment (except those collected after participant's withdrawal of consent) will be considered treatment-emergent. Similarly, the on-treatment period for the participants are defined as the whole study period from dose on Day 1 to EOS.

2.1.2 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. For multiple assessments performed at different time points on the same day (e.g. 0.5h, 1.5h and 4h on Day 1), there's no need to remap the time points and analysis will be performed based on the site collected time points.

[redacted]

The visit window below in Table 2-1 will be applied for efficacy endpoints (e.g. MADRS, [redacted]), safety endpoints (e.g. vital signs, C-SSRS and MOAA/S) and [redacted].

Table 2-1 Analysis visit windows (except for Lab and ECG)

Study visit	Target day (time)	Study day window
Baseline	1 (-1h)	Day -28 to Day 1 predose
Day 1	1	1
24 hours	2	2
Day 8	8	3 - 11
Day 15	15	12 - 18
Day 22	22	19 - 25
Day 29	29	26 - EOS

Laboratory assessments are only measured on Baseline, 24 hours post-dose on Day 2 and Day 29 (EOS), the visit window is listed in Table 2-2. ECG assessments are measured similarly as Lab with additional measures on Day 1(0.5h, 1.5h and 4h post-dose), the visit window is listed in Table 2-3.

Table 2-2 Analysis visit windows for Laboratory

Study visit	Target day (time)	Study day window
Baseline	1 (-1 h)	Day -28 to Day 1 pre-dose
24 hours	2	Day 1 post-dose to Day 4
Day 29	29	5 - EOS

Table 2-3 Analysis visit windows for ECG

Study visit	Target day (time)	Study day window
Baseline	1 (-1 h)	Day -28 to Day 1 pre-dose
Day 1	1 (0.5 h, 1.5 h, 4 h)	Day 1 post-dose to end of Day 1
24 hours	2	Day 2 to Day 4
Day 29	29	5 - EOS

By-visit summary will be provided for the efficacy and safety endpoints [redacted] based on the scheduled visits. No prioritization of scheduled vs unscheduled visit will be made. In case of multiple assessment values among the same type of visit (i.e., scheduled vs. unscheduled) 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.

All results collected during study visits (scheduled or unscheduled) will be displayed in listings.

2.2 Analysis sets

The **Randomized set** includes all randomized participants.

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

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

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

The number and percentage of patients in each analysis set will be summarized.

The primary analysis and other analysis for other efficacy outcomes (including [redacted]) will be performed on the FAS and the SAF will be used for all analysis of safety outcomes.

Rule of exclusion criteria of analysis sets (For GenMeds use only): See Appendix 5-5.

[redacted]

2.3 Other antidepressants or any combinations Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Participants' disposition will be assessed at screening and at the end of study.

The number of participants screened and rescreened will be reported. Subject dispositions at the end of screening phase will be summarized. The primary reason for not completing the screening phase will also be summarized.

Information on inclusion and exclusion criteria will be provided for subset of screened patients not continuing to randomization.

The number and percentage of participants who completed study will be summarized based on FAS. For early study discontinuations, the reasons will be summarized.

The details of the screening and study dispositions will be listed at subject level.

The number of patients randomized will be summarized by country.

For protocol deviation (PD), the number and percentage of participants will be provided by PD category and deviation term and summarized for each arm. All PDs will be listed by treatment arms and by PD categories.

2.3.2 Demographics and other baseline characteristics

Demographic variables and other baseline characteristics will be summarized for each randomized treatment arm and for all participants (total) based on Randomized set.

Participant demographic and baseline characteristics will include:

- Age
- Sex
- Ethnicity
- Race
- Height
- Weight
- BMI and BMI group (<25; >=25 and <30; >=30)
- Employment status
- Social status
- Region (USA, Europe, Japan)

Disease characteristics at baseline will include:

- Drug class of baseline antidepressants: Selective Serotonin-Reuptake Inhibitors (SSRIs); Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs); Other antidepressants or any combinations

- Baseline SoC category: Antidepressant in monotherapy; Antidepressants in combinations; Antidepressants + Augmentation
- CYP2D6 metabolizer phenotypes classifications (Ultrarapid metabolizers, Normal metabolizers, Intermediate metabolizers, Poor metabolizers)
- Baseline MADRS score and category (<30, 30-34, 35-40, >40)
- Disease duration (years) derived as (randomized date – Date MDD first ever diagnosed) / 365.25
- Duration of current depressive episode (weeks) derived as (randomized date – onset date of current depressive episode) / 7
- Total number of major depressive episodes in lifetime (excluding the current episode): 1, 2, 3-5, >5
- Overall severity of current episode (mild, moderate, severe, not reported)
- Overall severity of the first episode (mild, moderate, severe, not reported)
- Hospitalization events for current episode (Yes/No)
- Does the participant have any biological relatives who have or had diagnosis of Psychiatric disorder (yes, no)
- Current major depressive episode features
  - Anxious distress (yes/no)
  - Mixed features (yes/no)
  - Melancholic features (yes/no)
  - Atypical features (yes/no)
  - Catatonia (yes/no)
  - Seasonal pattern (yes/no)
- Number of failed antidepressant treatments prior to screening in current MDE (<3, >= 3).
- Reason for discontinuation of prior MDD related medication/therapies (due to lack of efficacy, adverse event, non-compliance, no longer required, others).

The antidepressant category of patients at baseline is summarized based on the actual baseline ADs collected in eCRF CM page, in the case that patient has no baseline antidepressant reported, the randomization strata from the IRT system will be used.

The baseline SoC category is summarized based on the number of ADs (monotherapy = only one AD; combinations = at least two ADs) and whether an augmentation therapy is used as combination therapy at baseline. The baseline SoC (AD or augmentation) is identified by CMCAT=" MDD RELATED MEDICATIONS" in CM data and the ADs are selected by ATC3="ANTIDEPRESSANTS". The augmentation therapies are reported with CMCAT=" MDD RELATED MEDICATIONS" in eCRF and confirmed during clinical review.

Demographic and other baseline data will be summarized descriptively by treatment arm for all study participants in the Randomized set.

2.3.3 Medical history and current medical condition

Any medical history and current medical conditions at baseline for all randomized patients will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT) and by treatment arm.

All previous major depressive episodes (including current MDE) will be collected for each patient. For the reported first and current MDEs, the following criteria will be used to impute the partial start dates, which will be used in calculation of the disease duration and the duration of current episode defined in Section 2.3.2.

- If year and month are present and day is missing (YYYY-MM-XX), impute the start date as YYYY-MM-15;
- If year is present and missing month and day (YYYY-XX-XX), use 01-July of that year (YYYY-07-01) as the start date.
- If completely missing, no imputation will be performed.

All collected information for MDEs will be listed at individual level and by treatment arms. No imputation is needed for the partial/missing start/end dates and the reported start/end dates will be used in the listing.

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

2.4.1 Study treatment / compliance

The study treatment is single injection of MIJ821 (10mg, 4mg or 1mg) or placebo on Day 1, the number of patients completed treatment will be reported by treatment arm based on SAF. Patients with protocol deviations related to treatment will be summarized in the PD summary table.

In case of unblinding during the study, any efficacy-related PRO data (including MADRS, [redacted]) collected after unblinding will be removed from the corresponding analysis. All safety data (including AE and safety-related PRO data) will be included in the corresponding analysis.

2.4.2 Prior, concomitant medications and non-drug therapies

For the standardization of data display, all the prior and concomitant medications reported on eCRF page will be coded using the World Health Organization (WHO) drug dictionary, which employs the Anatomical Therapeutic Chemical classification (ATC) system. The version of the dictionary used will be reported in the TFL outputs.

Non-drug therapies or procedures will be coded by Medical Dictionary for Regulatory Activities (MedDRA).

All analysis for prior and concomitant medications will be performed based on the safety set SAF.

The prior medications/non-drug therapies are defined as drugs/non-drug therapies taken and stopped before the start of the study treatment on Day 1. Concomitant medications/non-drug therapies are defined as drugs taken at least once after the study treatment on Day 1.

For missing start or stop dates of the reported medications, the dates will be imputed using Novartis standards (Section 5.1.3).

Prior and Concomitant medications will be summarized separately based on ATC code (level 1 and level 3), preferred term and treatment arm.

Prior MDD-related medications will be summarized based on ATC code (level 1, 3 and 4), preferred term and treatment arm.

Prior and Concomitant non-drug therapies will be summarized separately by primary system Organ Class and preferred term.

2.4.2.1 Current Standard of care (SoC) and psychotherapy use

Current standard of care (SoC) is identified as (1) medications flagged as "MDD related medications" on the 'prior or concomitant medication' e-CRF page, (2) ongoing during treatment (i.e. started before first dose of study drug and ongoing thereafter) and (3) the medication is either an antidepressant (ATC3="ANTIDEPRESSANTS") or an augmentation drug as confirmed by clinical review.

Psychotherapy is allowed to be used and needs to be stable during the study. Current allowed MDD related procedure (Psychotherapy) is identified as (1) flagged as "MDD related procedures" on the 'prior or concomitant non-drug therapies/procedures' e-CRF page, (2) is NOT listed in the prohibited medication table ([Table 6-2] in the protocol) and (3) ongoing during treatment (i.e. started before first dose of study drug and ongoing thereafter).

Current standard of care (SoC) medications will be summarized by ATC code level 1, 3 and 4 and preferred term and by treatment arms. Current allowed MDD related procedure will be listed by treatment arms.

2.4.2.2 Intercurrent events

Medical review will be conducted to identify intercurrent events (IE) with onset happen post-dose, especially before the 24 hours post-dose assessment of the primary outcome (MADRS score). A listing of any new/change in medication/therapies post the treatment will be generated for this purpose and the records happened within 24 hours post-dose will be marked. Intercurrent events may include:

- New intake or change in baseline SoC medications/therapies which have a potential confounding effect.
- Intake of prohibited medication/ therapy [redacted]
- Intake of rescue medications.

The rescue medications are identified by clinical judgement based on documented usage and indication of the drug. List of rescue medications (if any) identified by clinical team during medical review before DBL will be used in the CSR outputs.

The listing of concomitant medications and therapies which qualify as intercurrent events with onset after injection on Day 1 will be provided and the records within 24 hours post-dose will be marked. The '24 hours post-dose' will be based on the actual assessment date/time of the efficacy outcome on Day 2. Different flags will be used to mark different IEs. For SoC changed before 24 hours post-dose assessment, all records of the same drug will be listed and the first record of change will be flagged. For prohibited/rescue medications, any use during 24 hours post-dose will be flagged.

2.5 Analysis supporting primary objective(s)

The primary efficacy analysis will be conducted after all required data are collected and cleaned.

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

2.5.1 Primary estimand and endpoint(s)

The **primary estimand** is described by the following attributes:

1. Population: participants with treatment resistant depression, who have failed to show adequate treatment response to at least 2 antidepressants previously.
2. Primary variable: change from baseline in MADRS total score at 24 hours post-dose
3. Treatment of interest: the randomized treatment (the investigational treatment MIJ821 or the placebo treatment) administered as a single s.c. injection on Day 1. The dose of the allowed concomitant medication (SoC) for depression must remain stable after baseline and during the trial.
4. Intercurrent Events (IEs) prior to MARDS assessment at 24 hours.
   IEs with potential confounding effect prior to the 24-hour assessment:
   - New intake or change in concomitant medications/therapies which have a potential confounding effect.
   - Intake of prohibited medications/therapies.
   - Intake of rescue medication.
   - Pandemic related IEs.
   - IEs leading to study discontinuation prior to the 24-hour assessment:
     - Adverse events (AE).
     - Lack of efficacy (LoE).
     - Other reasons for study discontinuation.
5. The summary measure: treatment difference in variable means between study drug and placebo.

The **primary endpoint** is the change from baseline in MADRS total score at 24 hours post study treatment.

2.5.1.1 Derivation of MADRS total score

The MADRS consists of 10 items that cover all the core depressive symptoms (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts). Each item is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptom). For each item, a higher score represents a more severe condition.

The MADRS score will be measured at Screening, Baseline (Day 1, -1 hour), 4-hour post-dose on Day 1, 24 hours post-dose and follow-up visits on Day 8, Day 15, Day 22 and Day 29 (EOS).

The 4-hour post-dose assessment will use the '4-hour' questionnaire which is based on participant's condition as observed over the past 4 hours. Two items (reduced sleep and reduced appetite) are not applicable for 4-hour post-dose assessment and will be imputed based on the value of respective 1-hour pre-dose assessment.

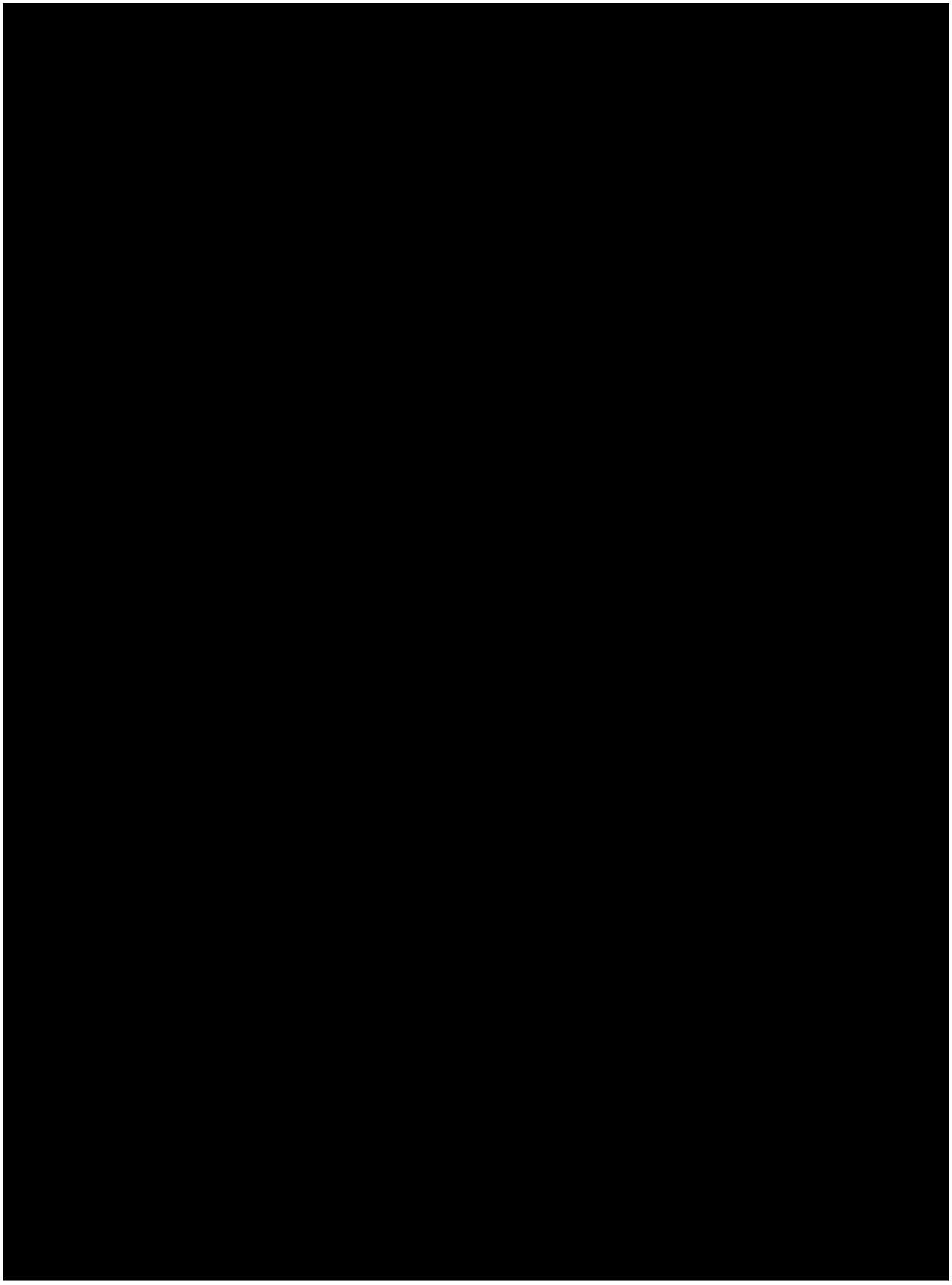
The 24 hours post-dose assessment is based on the participant's condition as observed since the last evaluation. For all other assessments, a 7-day recall period is used.

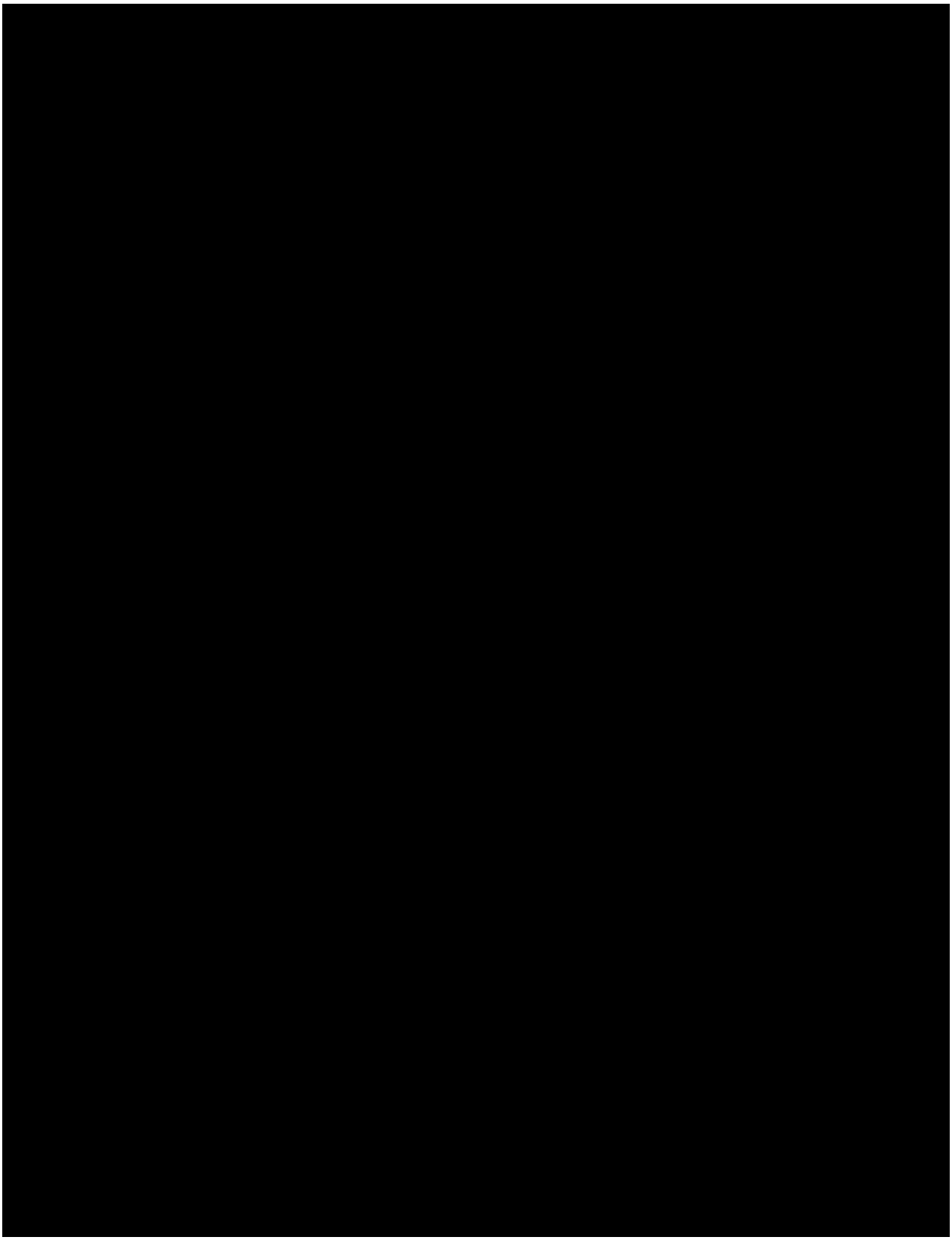
A total score (ranges from 0 to 60) is calculated by adding the scores of all 10 items. The following proration formula will be applied to calculate the total score in the case when one of the item scores is missing:

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

Otherwise if 2 or more items are missing, the total score will be set to missing.

[redacted]





[redacted]

2.5.4 Handling of missing values not related to intercurrent events

For other missing outcomes caused by reasons other than IEs, multiple imputation approach will be applied assuming MAR for all treatment arms.

[redacted]

2.6 Analysis supporting secondary objective(s)

2.6.1 Efficacy endpoint(s)

2.6.1.1 Duration of antidepressant effect of MIJ821

Change from baseline in the MADRS total score over time

Derivation of the MADRS total score is covered in Section 2.5.1.1. The change from baseline in MADRS total score will be summarized for all collected data (including 4-hour post-dose) by visit/timepoint and by treatment arms. In case of unblinding, the MADRS scores collected after patient's unblinding will be excluded in all the analysis. A listing of MADRS total score for each participant at each visit will be provided by treatment arm.

The change from baseline in MADRS total score at follow-up visits on Day 1 4 h post-dose, Day 2, 8, 15, 22 and 29 will be analyzed using the mixed-effects model for repeated measures (MMRM). This model will include the fixed, categorical effects of treatment, time (i.e. analysis visits), baseline MADRS score, class of anti-depressant standard of care, treatment-by-time and baseline MADRS score-by-time interactions. [redacted]

A summary table with model estimated means and their differences of each MIJ821 doses vs. placebo, will be obtained at each visit/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 each arm.

[redacted]

2.7 Safety analyses

The safety and tolerability of MIJ821 will be evaluated by adverse events, clinically significant findings from laboratory test, physical examination, vital signs, 12-lead ECG. Abnormal findings from safety scales will be reported as adverse events and analyzed accordingly. For all safety analysis, the safety set (SAF) will be used. All listings and tables will be presented by treatment arm.

The treatment-emergent period will be defined as starting from the date of administration of study treatment to EOS visit. Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). Treatment-Emergent Adverse Events (TEAEs) in this study are defined as adverse events starting or worsening after the administration of study medication and up to the EOS visit. That is, all the reported AEs collected post treatment will be considered as TEAEs, so we will simply use AEs all through this section to avoid any confusion.

2.7.1 Adverse events (AEs)

The missing onset date of AE will be imputed using the Novartis standard imputation rules (Section 5.1.2).

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later will be used to code Adverse Event (AE) to a SOC and a PT. The version used will be displayed in the table footnote.

The number (and percentage) of participants with AEs will be summarized by following approach as defined in Table 2-6, in terms of all AEs, Serious Adverse Events (SAEs), treatment-related AEs or SAEs and fatal AEs that caused death:

- by treatment arm, primary system organ class and preferred term
- by treatment arm, primary system organ class, preferred term and maximum severity
- by treatment arm, preferred term with most frequency (incidence rate > 10%)

Table 2-6 AE summaries

Category	by SOC and PT	by SOC, PT and maximum severity	by most frequent PT (≥ 10%)
All AEs	Y	Y	Y
SAEs	Y		
All treatment-related AEs	Y	Y	
Treatment-related SAEs	Y		

For all AE tables presented by SOC and PT, 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. If a particular AE severity is missing, the variable will be listed as missing and treated as missing in summaries. If a participant reported more than one AE within the same SOC, the participant will be only counted once and the AE with greatest severity will be presented. Similar approach will be used to handle the situation of multiple AE within the same PT for the same participant.

The time to onset of AEs will be summarized by PT by descriptive statistics.

All AEs and SAEs will be listed separately at individual level and by treatment arms.

Participants with any abnormal findings (worsening or newly occurring) in AE will be listed by treatment arms. This listing is used to evaluate the withdraw/rebound effect of MIJ821 after 2 weeks of the treatment. A 'newly occurring AE' is defined as an AE that did not happen between treatment on Day 1 and the 2 weeks follow-up afterwards but happened after 2 weeks. A 'Worsening AE' is defined as an AE happened between treatment and 2 weeks in follow-up, and the severity increased after 2 weeks. Note that the actual Day 15 visit time will be used for the 2-week cut-off time point.

2.7.1.1 Clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and European Union Drug Regulating Authorities Clinical Trials (EudraCT), following summaries listed in Table 2-7 will be provided.

Table 2-7 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 with 0-5% threshold	Y	Y
	Number of Non-SAEs (0-5% threshold) by SOC/PT	Y	Y
	Number of occurrences of Non-SAEs with 0-5% threshold by SOC/PT		Y

2.7.1.2 Adverse events of special interest / grouping of AEs

The Adverse Events of Special Interest (AESI) is based on the availability of incremental clinical experience with MIJ821 and identified during safety review in electronic Compound Case Retrieval Strategy (CRS). MedDRA search criteria for AESIs will be identified by the latest version of CRS.

AESI will be summarized by risk and by PT for each treatment arm for the on-treatment period.

In addition, the investigator reported AESIs from the eCRF will be summarized similarly by risk and by PT and treatment arms.

The time to onset (starting from dosing on Day 1) and time to resolution (starting from first onset date) of each AESI will be summarized by descriptive statistics. Separate summary tables will be provided for AESIs started on dosing day (within 24 hours post-dose) and overall. In the case if a patient has multiple AESIs, the earliest starting time will be summarized for onset time and the latest end time will be used in summary of resolution time for that patient. The dot plot based on the onset time of each AESI at individual patient level will be provided for AESIs started on dosing day (within 24 hours post-dose) and overall.

Listing of the above AESI will be provided at participant level and by treatment arms for both AESIs identified by CRS and investigator reported, separately.

2.7.2 Deaths

Deaths (if any) will be summarized and listed under SAE by actual treatment arm.

2.7.3 Laboratory data

Both of raw measures and change from baseline of laboratory results (hematology, blood chemistry) will be summarized by treatment arm and analysis visit.

The clinical abnormality is defined as out of the normal ranges defined in the laboratory specification document. The newly occurring and worsening events are defined by comparing the measured laboratory parameters at baseline and post-baseline with the lower and/or upper limits of the normal ranges (see Table 2-8). In addition to the normal ranges, some of the lab parameters, which are covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, will also be graded using the Novartis internal validated macro (with details covered in PDS) and the newly occurring and worsening events are also defined in Table 2-8. The number and proportion of participants with newly occurring or worsening laboratory parameters based on normal ranges and CTCAE grades (if applicable) will be summarized by treatment arms and by visits (24 hours post-dose and EOS).

Table 2-8 Criteria for newly occurring or worsening laboratory parameters

	Event	Baseline	Post-baseline
Under CTCAE grades	Newly occurring	Grade 0 (normal)	Grade 1 - 4 (any abnormal)
		Missing	Grade 1 - 4 (any abnormal)
	Worsening	Grade 1	Grade 2 - 4
		Grade 2	Grade 3 - 4
		Grade 3	Grade 4
Under normal ranges	Newly occurring	Within normal range	< LLN or > ULN
		Missing	< LLN or > ULN
		< LLN	> ULN
		> ULN	< LLN
	Worsening	BSL < LLN	VALUE < BSL < LLN
		BSL > ULN	VALUE > BSL > ULN

BSL = Baseline value; LLN = Lower limit of normal range; ULN = Upper limit of normal range.

Participants with any abnormal findings in laboratory values (newly occurring or worsening) will be listed by treatment arm. For parameters with CTCAE definitions, the CTCAE grades will be added in the listing and records with CTCAE grade of 3 or 4 will be flagged.

To evaluate the potential drug-induced hepatotoxicity and renal signal, the liver and renal abnormalities at any time post-baseline will be analyzed by:

- the number and proportion of participants with any newly occurring liver enzyme abnormalities based on each criterion defined in Table 5-1 in Appendix.
- the number and proportion of participants with any renal abnormalities based on each criterion defined in Table 5-2 in Appendix.
- listings of participants with clinically liver or renal abnormality.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

2.7.4.1.1 Summary statistics of ECG parameter

Summary statistics of ECG parameters (PR, QRS, QT, QTcF and RR intervals) recorded centrally will be presented by treatment and visit/time.

2.7.4.1.2 Overall interpretation of the ECGs- ECG findings

Recording of ECG finding (e.g., prolonged QTc, Torsade de Pointes, Ventricular Tachycardia, etc.) will be sent to Novartis by the central ECG vendor.

ECG findings will be listed by treatment arm and visit/time.

2.7.4.1.3 Clinically significant change in ECG parameters

The incidence of abnormal ECG diagnosis (see Table 5-4 in appendix) will be presented in terms of count and percentage by treatment arm and by analysis visit.

Participants with abnormal ECG values will be listed by treatment arms and by visit, and the worsening or newly occurring cases will be marked in the listing.

Box plot for change from baseline of QTcF parameter will be provided by treatment arms and by visit.

2.7.4.2 Vital signs

The analyses of vital signs (body temperature, systolic/diastolic blood pressure, pulse rate) and weight will include summary statistics for both the original measures (averaged means of three measures) and the change from baseline by treatment arm and by analysis visit. Boxplot and Mean+/-SD line plot of the change from baseline of blood pressure (SBP and DBP) over time will be provided by treatment arm.

The number and percentage of participants with clinically relevant abnormality (see Table 5-3 in appendix) at any post-baseline visit will be presented.

Participants with clinical relevant abnormality and any abnormal findings (worsening or newly occurring) will also be flagged in listings.

2.7.4.3 Clinician Administered Dissociative States Scale

The Clinician Administered Dissociative States Scale (CADSS) is a questionnaire that assesses dissociative effects might related to MIJ821. The CADSS comprises 23 subjective items and participant's responses are coded on a 5-point scale (0=" Not at all", 1=" Mild", 2="Moderate", 3="Severe" and 4="Extreme") based on their current experience. The CADSS will be assessed at baseline (Day 1, -1 hour pre-dose), 0.5 hour, 1.5 hour and 4-hour post-dose on Day 1, and follow-up assessments at Day 2 (24-hour), Day 8, Day 15, Day 22 and Day 29.

The CADSS can be divided into 3 components using the following scoring method defined in Table 2-9. A higher score represents a more severe condition. Missing data at any subjective item will be unlikely since the items could not be skipped during the interview unless raters provide rationales, in which case the component scores and the total score will be calculated based on the proration approach. Specifically, if the percentage of missing items is more than 10% of the total number of items for the component score, no imputation will be made and the component score will be missing. Otherwise, the sum of available items will be used and the component score is calculated as follows:

Component score = Sum of scores from items present*(total number of items in the component/number of items present).

Table 2-9 CADSS components and total scales

Component	Questions	Range
Depersonalization	Sum of 3, 4, 5, 6, 7, 20, 23	0-28
Derealization	Sum of 1, 2, 8, 9, 10, 11, 12, 13, 16, 17, 18, 19, 21	0-52
Amnesia	Sum of 14, 15, 22	0-12
Total Score	Sum of 1 through 23	0-92

For the total score and each component score (depersonalization, derealization and amnesia), the summary table of original measures and change from baseline values will be provided by treatment arm and analysis visit. The component scores for patients with CADSS total score >0 at any post-dose visit will be listed. Boxplots will also be provided for change from baseline values for the total score over time by treatment arms.

In addition, the number and percentage of participants satisfying the following criteria will be summarized separately by treatment arms and by analysis visit.

- CADSS total score > 4 and change from baseline > 0.
- Change from baseline in CADSS total score > 4.

2.7.4.4 Modified Observer's Assessment of Alertness/Sedation

The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) will be used to assess participant responsiveness and measure sedation associated with MIJ821. The MOAA/S scores

range from 0 [No response to painful stimulus] to 5 [Readily responds to name spoken in normal tone (awake)]. A lower score of MOAA/S indicates more severe condition of sedation.

The MOAA/S will be taken at the same visits and time points as CADSS. The following summary table and/or plots will be provided:

- A stacked bar plot for categorical MOAA/S score by treatment arm and analysis visit.
- Summary table and bar-plot comparing the percentage of participants with any sedation (MOAA/S<=4) across treatment arms over time.
- Summary table and bar-plot comparing the percentage of participants with severe sedation (MOAA/S<=2) across treatment arms over time.

2.7.4.5 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses suicidal ideation and behavior (SIB) and non-suicidal self-injurious, as well as intensity assessments for suicidal ideation, as summarized in Table 2-10 below. The 11 preferred SIB categories include five levels of suicidal ideation, five levels of suicidal behavior and the category non-suicidal self-injurious. Each category has a binary response (yes/no). For this study, participants who have suicidal ideation with intent (answered 'Yes' for question 4 or 5) at baseline will be excluded from the study as screening failure.

The C-SSRS will be assessed at Screening, Baseline (Day 1, -1 hour pre-dose), 4-hour post-dose on Day 1, and follow-up visits at 24 hour (Day 2), Day 8, Day 15, Day 22 and Day 29 (EOS). The SIB assessments obtained during screening will be based on participant's experience during lifetime and past 1 month. All follow-up visits will be based on participant's experience since last visit.

The analysis for this scale will be based on the SAF. No safety cut-off will be applied for the SIB data reporting, i.e., all collected data will be used in the analysis.

Patients who answered "yes" to each question in Table 2-10 will be counted by treatment arm and by visit. The descriptive statistics will be provided for the suicidal ideation score (the most severe suicidal ideation) by treatment arm and by visit.

Suicidal ideation and behavior data will be listed. Detailed answers to C-SSRS items will be listed separately for subjects with any suicidal ideation at any time post-baseline (i.e., a 'yes' answer to at least one of the five suicidal ideation questions at any time post-baseline) and for a subject with any suicidal behavior at any time post-baseline (i.e., a 'yes' answer to at least one of the five suicidal behavior questions at any time post-baseline).

Table 2-10 C-SSRS components

Category number	C-SSRS category
Suicidal Ideation	
1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act
4	Active suicidal ideation with some intent to act, without specific plan

Category number	C-SSRS category
5	Active suicidal ideation with specific plan and intent
Suicidal behavior	
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt
9	Actual attempt
10	Completed suicide
Self-injurious behavior, without suicidal intent	
11	Non-suicidal self-injurious behavior

2.7.4.6 Amnesia/ memory gaps

For participants who have amnesia reported as AE after completing the memory assessment questions, the memory gap eCRF page will be filled.

A listing will be provided for participants with memory gaps by treatment arms.

2.8 Pharmacokinetic endpoints

2.8.1 Variables

Pharmacokinetic (PK) plasma samples will be collected from each study participant in accordance with the assessment schedule to determine the MIJ821 concentration. Only samples from participants treated with MIJ821 will be analyzed. Concentrations will be expressed in mass per volume units.

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

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

2.8.2 Descriptive analyses

In addition to the commonly used statistics, additional statistics will be used for summarizing the PK endpoints. The N values are defined as the number of participants with valid measures in each dose arms in the PK analysis set. The %CV (coefficient of variation percent) values will be summarized using the arithmetic mean calculated as ‘100*(standard deviation / mean)’ and the geometric mean calculated as ‘sqrt (exp (variance for log transformed data)-1)*100’.

All MIJ821 plasma concentrations and PK parameters including their descriptive statistics will be presented with three significant figures. The exception will be %CV values, which will be reported to one decimal place and N values, which will be reported as whole integers.

Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

Concentrations

- will be listed by dose, subject, nominal sampling time and actual sampling time and containing information on body weight, age, gender, genotype classification
- will be graphically presented as concentration-time course per individuum (individual plot per graph, linear-linear and log-linear plots)
- will be graphically presented as concentration-time course per dose as spaghetti plot (overlying individuum courses, linear-linear and log-linear plots)

Summary statistics of concentrations by dose and nominal time

- will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum, N values, and the frequency (n, %) of concentrations below the LLOQ. A geometric mean will not be reported if the dataset includes zero values.
- will be graphically presented as concentration-time courses of arithmetic means and nominal times (SD) by dose (overlaying, linear-linear and log-linear plots)

PK parameters

- will be listed by dose and subject and containing information on body weight, age, gender, genotype classification

Summary statistics of PK parameters by dose

- will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum, and N values. 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.

[redacted]

[redacted]

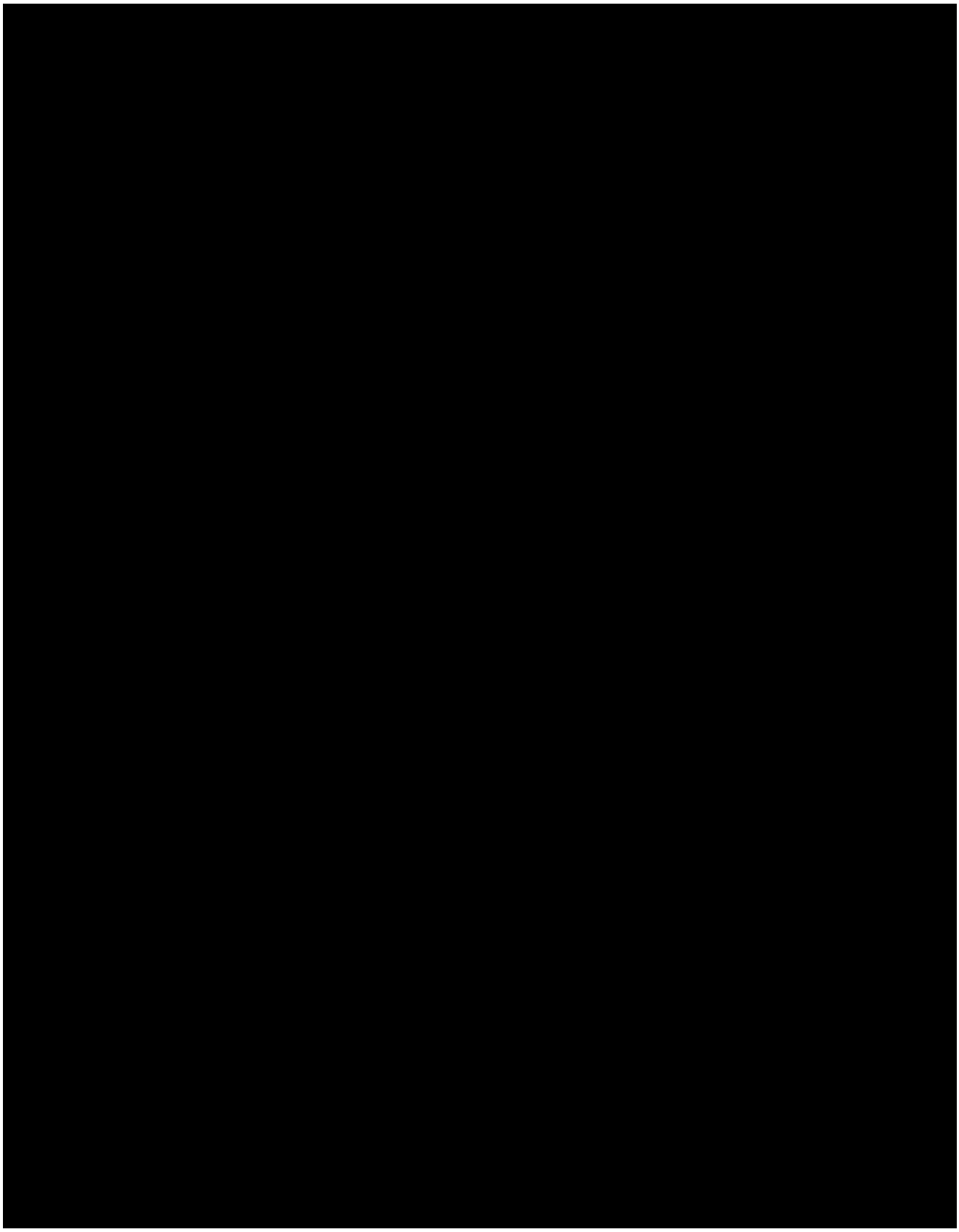
2.9 PD and PK/PD analyses

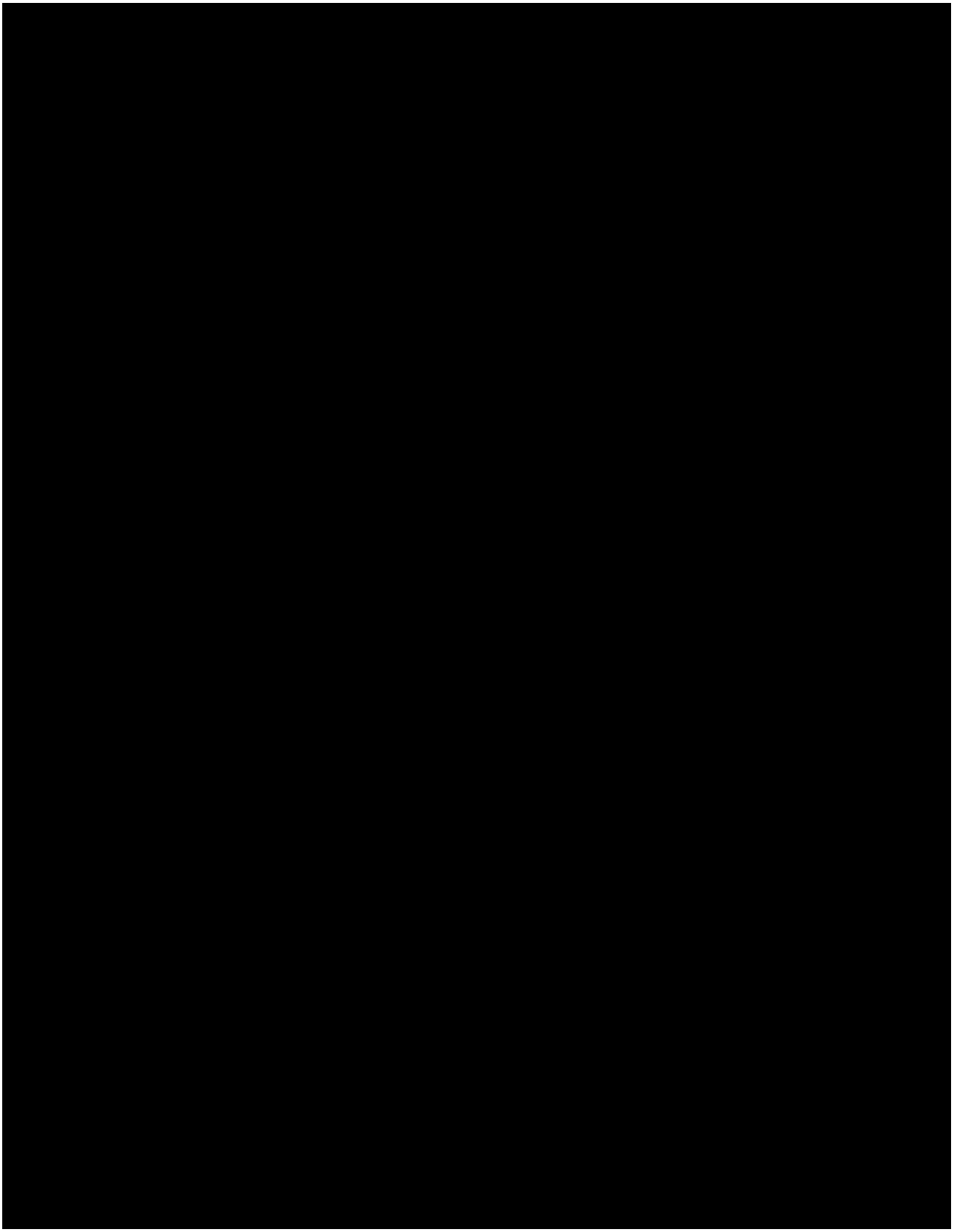
The exposure response relationship will be presented graphically for PK exposure parameters (e.g. Cmax and AUClast) and the change from baseline MADRS score derived at 24 h postdose and Day 8, Day 15, Day 22 and Day 29 during the follow-up.

Correlations will be assessed using statistical analysis methods (e.g. trendline analysis methods) and simple exposure response models (e.g. Sigmoid Emax models). Scatter plots of change from baseline of MADRS score (y-axis) versus PK exposure parameter (x-axis) will be provided by visit and the fitted lines and 90% pointwise confidence intervals from both the trendline analysis and Sigmoid Emax model will be added in the plots separately for each visit.

The hill parameter in the Sigmoid Emax models will be estimated if data allows. In case the model dose not converge, the Emax model with hill parameter equals 1 will be used. A table with estimated placebo effect and estimated parameters from the Sigmoid Emax models will be presented by visit.

[redacted]





[redacted]

3 Sample size calculation

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

The six candidate DR curves (6 Sigmoid Emax) for power calculation are defined in Section 2.5.2. [redacted]

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Missing or partial start/stop dates for AE will be listed as it is in the associated listings.

For analysis that needs to use the start date of an AE, e.g. in determination of whether an AE is treatment-emergent, the details will be provided in the programming dataset specification (PDS).

5.1.3 Concomitant medication date imputation

Missing or partial start/stop dates and time for concomitant medication will be listed as it is in the associated listings.

For analysis that needs the start date and time of concomitant medication, the details of date/time imputation will be provided in the programming dataset specification (PDS).

5.1.3.1 Prior therapies date imputation

For prior medications with a stop date prior to Day 1, the start date will be imputed as the earliest possible start date and the stop date as the latest possible stop date. More details will be covered in the PDS.

5.1.4 Baseline SoC categories

The summary of baseline standard of care is based on the categories of antidepressants (ADs) and augmentation therapies. Since some of the drugs of interest (e.g., SNRIs) cannot be identified based on the available ATC codes, and some augmentation therapies rely on the clinical review. A list of the drug class of interest (SSRI, SNRI, Other AD and Augmentation therapy) will be provided as a result of the clinical review on our blinded CM data and used for programming of the outputs. More details will be provided in the PDS.

5.2 AEs coding/grading

The reported terms of adverse events will be coded by primary system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) with version 25.0 or above.

5.3 Laboratory parameters derivations

The grading for most of the lab parameters collected in hematology, chemistry, urinalysis and coagulation are defined using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The grading criteria for these parameters are adapted in a validated Novartis macro

and will be applied to the lab parameters to derive the CTCAE grades. Note that the macro is based on a simplified version of the CTCAE criteria considering programming feasibilities, e.g.:

- For certain laboratory parameters the CTCAE grade definition was simplified in the macro to rely on laboratory results only (i.e., information from adverse events and/or other clinical assessment are not considered in the definition of CTCAE terms).
- For laboratory parameters that depend on baseline values, the Novartis macro simplified the rule to have the grade only defined on normal range limits (LLN or ULN) value without considering the baseline values. This is a conservative approach and allows grading of post-baseline values even if baseline values are missing.

More details of the CTCAE macro will be provided in the PDS.

Liver abnormality are defined using the criteria listed in Table 5-1. The following are covered: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms upper limit of normal.

Table 5-1 Liver abnormality criteria

	Definition/ threshold
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 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 > 200 U/L (whichever occurs first)

*ULN: upper limit of normal

Table 5-2 Renal abnormality criteria

Criterion
Serum creatinine increase ≥25% and <50% compared with baseline
Serum creatinine increase ≥50%
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or 113 mg/mmol Cr equivalent as converted by the measuring laboratory)
New onset hematuria ≥ 3+ on urine dipstick

Table 5-3 Clinically notable values for vital signs

Table	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; increase of ≥ 40 mm Hg
Diastolic blood pressure	≥105 mm Hg; ≤50 mm Hg	increase of ≥ 15 mm Hg; decrease of ≥ 15 mm Hg; increase of ≥ 25 mm Hg

*bpm= beats per minute

Table 5-4 ECG abnormality criteria

ECG Parameter	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	Low: ≤ -20%; High: ≥ 20%
QT Interval	Low: < 320 msec ; High: >= 450 msec for male, >=460 for female; > 500 for both	High: >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	High: >30 to <=60 msec, >60 msec

*Relative change in percent (%) for RR, PR and QRS intervals, relative change in values in millisecond (msec) for QT and QTcF Interval. Relative changes are compared with baseline assessment for all ECG parameters.

[redacted]

[redacted]

[redacted]

5.5 Rule of exclusion criteria of analysis sets

Table 5-5 Participants classification

Analysis Set	Criteria that cause subjects to be excluded
FAS	Not randomized
	Mistakenly randomized and no double-blind study drug taken
SAF	No double-blind study drug taken

6 Reference

Bretz F, Pinheiro JC, Branson M (2005) Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics: 738-48.

Rubin, D. B. (1976). Inference and missing data. Biometrika, 63(3), 581-592.

Rubin, D. B. (2004). Multiple imputation for nonresponse in surveys (Vol. 81). John Wiley & Sons.