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Biostatistics & Statistical Programming /
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MIJ821

CMIJ821X2201

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

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The Reporting and Analysis Plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"*CMIJ821X2201*".**

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

Study protocol (v02) is available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1. Primary objective(s)

Primary objective(s)	***Endpoints related to primary objectives***
• To assess efficacy of MIJ821 in treatment-resistant depression.	• Montgomery Asberg Depression Rating Scale (MADRS) total score at 24 hours after the start of the infusion compared to the baseline assessment.

1.3.2. Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objectives***
• To assess risk of mania induction	• Young Mania Rating Scale at 24 hours, 48 hours (if applicable) and 6 weeks post-dose.
• To assess efficacy in the melancholic subtype of depression.	• Bech-Rafaelsen Melancholia and CORE scale change from baseline to 24 hours, 48 hours (if applicable) and 6 weeks post-dose.
• To assess safety and tolerability, especially dissociative side effects.	• Incidence of adverse event • Dissociative rating scales (Clinician-Administered Dissociative States Scale, and Dissociative Experiences Scale) change from baseline to 24 hours, 48 hours (if applicable) and 6 weeks post-dose.
• To assess most effective dose and dosing regimen.	• Montgomery Åsberg Depression Rating Scale score at 6 weeks.
• To assess MIJ821 pharmacokinetics in plasma	• PK properties of MIJ821 in plasma described by AUClast, AUC0-24h,

	Cmax, Tmax (parameters not limited)
• To assess impact of MIJ821 on suicidality	• Sheehan Suicidality Tracking Scale changes from baseline at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion.
• To assess efficacy of MIJ821 on measures of response and remission	• % treatment response (>50% improvement in MADRS) at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion. • % treatment remission (MADRS<7) at 24 hours, 48 hours (if applicable_, and 6 weeks after the start of first infusion • CGI-S and CGI-I scores at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion
• To assess efficacy of MIJ821 for mixed mood symptoms.	• Koukopoulos Mixed Depression Rating scale change from baseline to 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion.
• To assess efficacy of MIJ821 for anxiety symptoms.	• Hamilton Anxiety Scale change from baseline to 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion
• To assess impact of mixed mood symptoms, melancholia, and anxiety as predictors of treatment response to MIJ821.	• Regression model effect sizes (odds ratios) for Hamilton Anxiety Scale, Bech-Rafaelsen Melancholia Scale, and Koukopoulos Mixed Depression Rating Scale as predictors, with MADRS treatment response as outcome, at 24 hours, 48 hours (if applicable), and 6 weeks after the start of first infusion.

1.3.3. Exploratory objective(s)

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1.4 Study design and treatment

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

Subjects will be randomized to the following 6-treatment arms (USA will not include ketamine arm)

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2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

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FIR will focus on the following analyses:

- Analysis populations (if needed)
- Subject disposition
- Demographics and baseline characteristics. Baseline characteristics include, but not limited to:
    - Body weight/height, BMI, age, sex, race, ethnicity, MADRS, Hamilton Anxiety Scale
- Safety results include but are not limited to:
    - Number and percentage of subjects with adverse events by body system and preferred term with a breakdown by treatment
    - Summary table presenting the frequency of subjects affected, time (in hours) of onset and resolution time (in hours) by treatment

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- Pharmacokinetic (PK) results for plasma (as appropriate, possibly using preliminary PK information with nominal collection times):

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- Efficacy/Pharmacodynamic (PD) analyses include, but are not limited to:

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3 Interim analyses

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4 Statistical methods: Analysis sets

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5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

5.1 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):

- AUClast, AUC0-24h, Cmax, Tmax, will be determined from the plasma concentration-time data.
- If PK data allows, secondary PK parameters will be estimated like T1/2, AUCinf, CL, Vz, Clast and Tlast (but not limited).

Samples collected from placebo and ketamine treated subjects will not be measured.

5.2 Descriptive analyses

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6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the ITT analysis set will be included in the ITT data analysis.

6.1 Primary objective

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

6.1.1 Variables

The primary variable is the change from baseline in the total MADRS score at 24 hours after single dose administration. At a given assessment time, the total MADRS score will be calculated as the summation of all scores from the ten items of the questionnaire across individual categories. Each item yields a score from 0 to 6, and thus the total score ranges from 0 to 60 for each individual.

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

6.1.2 Descriptive analyses

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6.1.3 Statistical model, assumptions and hypotheses

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6.1.3.1 Model checking procedures

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6.1.4 Sensitivity analyses

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6.1.5 Supportive analyses

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6.2 Secondary objectives

6.2.1 Variables

The secondary PD variables for this study are:

- change from baseline in the total MADRS score at 6 weeks after repeated dose administration.
- change from baseline in "Suicidal Thoughts" item at 6 weeks after repeated dose administration
- change from baseline in the total Bech-Rafaelsen Melancholia scale at 24 hours, 48 hours (as appropriate), and 6 weeks post-dose.
- change from baseline in the total CORE Melancholia scale at 24 hours, 48 hours (as appropriate), and 6 weeks post-dose
- change from baseline in the total Koukopoulos Mixed Depression Rating scale 24 hours, 48 hours (as appropriate), and 6 weeks after the start of first infusion
- change from baseline in the total Hamilton Anxiety scale 24 hours, 48 hours (as appropriate), and 6 weeks after the start of first infusion
- change from baseline in the total Young Mania Rating scale at 24 hours, 48 hours (as appropriate), and 6 weeks post-dose.
- change from baseline in the total Clinical Global Impression-Severity (CGI-S) score at 24 hours, 48 hours (as appropriate), and 6 weeks after the start of first infusion

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

- Clinical Global Impression-Improvement (CGI-I) total score at 24 hours, 48 hours (as appropriate), and 6 weeks after the start of first infusion
- proportion of treatment response (>50% improvement in MADRS) at 24 hours, 48 hours (as appropriate), and 6 weeks after the start of first infusion
- proportion of treatment remissions (subjects with MADRS < 7) at 24 hours, 48 hours (as appropriate), and 6 weeks after the start of first infusion

6.2.2 Descriptive analyses

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6.2.3 Statistical model, assumptions and hypotheses

6.2.3.1 MMRM analyses

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6.2.3.2 Proportion of responders

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6.2.3.3 Regression model effect sizes

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6.3 Exploratory objectives

6.3.1 Variables

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6.3.2 Descriptive analyses

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7 Statistical methods for safety and tolerability data

All subjects within the Safety analysis set will be included in the safety data analysis.

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, Sheehan suicidality scale score, as well as subject demographics, baseline characteristics, and treatment information.

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

7.1.1 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

The below descriptive analysis will be conducted on the following two blood pressure (BP) parameters and their change from baseline: SBP and DBP.

- A separate summary statistics (quantitative) of raw values and change from baseline values will be provided by treatment group and timepoint.
- Summary tables of categorical analyses will be produced displaying the number and percentage of subjects with notable BP observations (irrespective of the timepoint) using the following categories:
    - SBP <90 mmHg;
    - SBP >140 mmHg;
    - SBP increase from baseline >20 mmHg;
    - SBP decrease from baseline >20 mmHg;
    - DBP <50 mmHg; DBP >90 mmHg;
    - DBP increase from baseline >20 mmHg;
    - DBP decrease from baseline >20 mmHg

  These categorical analyses will be provided for each treatment group

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  For criteria with change from baseline, only measurements occurring after 1st injection on Day 1 will be included. For other criteria, both baseline and post-baseline measurements will be included. All scheduled and unscheduled visits will be used for this summary table.

ECG evaluations

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

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

Adverse events

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

Summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

The number and percentage of subjects with adverse events and drug-related adverse events will be separately tabulated, by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

In addition, the number and percentage of subjects with adverse events will be tabulated by body system, preferred term, maximum severity with a breakdown by treatment group. A subject with multiple severity ratings for an AE under treatment, is only counted under the maximum rating.

Summary tables to show the frequency of subjects affected, time (in hours) of onset and resolution time (in hours) by treatment (MIJ821 0.16 mg/kg pooled, MIJ821 0.32 mg/kg pooled and placebo) and total, will be provided for AEs of interest (dissociation, amnesia, dissociation and amnesia (together), sedation and vomiting).

For these summary tables of AEs of interest, the following guidelines will be applied:

1. Frequency / time to onset / time to resolution of AEs of interest:
    - Frequency - A subject with multiple AEs with the same preferred term (PT) is counted only once for that PT
    - Time to onset – A subject with multiple events in a preferred term of interest, we are only considering the first instant
    - Time to resolution – A subject with multiple events in a preferred term of interest, we are only considering the maximum of the AE duration

2. For subjects who experienced ‘Dissociation and amnesia’:
    - Time to onset – we will use time to 1st instant (whether it’s dissociation or amnesia)
    - Time to resolution – we will use maximum of the AE duration (whether it’s dissociation or amnesia)

3. Based on the consultation with the clinical team, the following rules for grouping of the AEs of interest were elicited:

AE of interest	Notes
Sedation	See AE grouping below
Dissociation	See AE grouping below + 'dissociative amnesia'
Amnesia	Any term that includes 'amnesia', except for 'dissociative amnesia' which falls under 'Dissociation'
Dissociation and Amnesia	Patients who experienced both amnesia and dissociation

	Applicant grouped:	We added:
Sedation	sedation; somnolence; altered state of consciousness; depressed level of consciousness; hypersomnia; stupor	loss of consciousness
Dissociation	dissociation; depersonalization/derealization disorder; derealization; dissociative disorder; flashback; hallucination; auditory hallucination; visual hallucination; illusion; somatic hallucination; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysesthesia; oral dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change	dysgeusia; dysmetropsia; feeling abnormal; feeling drunk; hyperesthesia; hypersensitivity; illusion; metamorphopsia; oral hyperesthesia; pharyngeal hypoesthesia; photopsia; photosensitivity reaction; synesthesia; altered visual depth perception; confusional state; delirium; hypogeusia; pain threshold decreased; hypoesthesia; eye hyperesthesia

Separate summaries will be provided for study medication related AEs, SAEs, other significant AEs leading to discontinuation.
In addition, a separate summary for death including on treatment and post treatment deaths will be provided.

For outputs of interim analyses, a safety window of adverse events occurring 48 hours after the 1st injection on Day 1, will be considered. All data for adverse events, as well as time of onset and resolution time for adverse events of interest, will be listed by treatment group and subject,

including non-treatment emergent adverse events and the treatment emergent adverse events occurring 48 hours after first injection on Day 1.

Relationship between dissociative, amnesia AE and MADRS total score

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ClinicalTrials.gov and EudraCT

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE. Subjects with treatment emergent SAEs and SAEs suspected to be related to study treatment, by system organ class and preferred term will be provided.

7.2 Other safety evaluations

7.2.1 Sheehan suicidality tracking scale score (S-STS)

Sheehan suicidality tracking scale (S-STS) is a fourteen-item (up to 22) scale. Each item in the S-STS is scored on a 5-point Likert scale (0=not at all, 1= a little, 2=moderately, 3=very, and 4=extremely). Data from the S-STS will be analyzed as individual item scores, suicidal ideation subscale score (sum of scores from items 2, 3 and 4, plus score from item 5 if ≤ 1), suicidal behavior subscale score (sum of scores from items 6, 7a and 8, plus score from item 5 if > 1). Items and scores (including the 2 subscales and the total score) data will be listed by treatment, subject and visit/time; abnormalities will be flagged.

7.2.1.1 Descriptive analyses

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7.2.2 Clinical-Administered Dissociative States Scale (CADSS)

7.2.2.1 Descriptive analyses

CADSS total score data will be listed by treatment, subject and visit/time; abnormalities will be flagged.

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7.2.2.2 Statistical model, assumptions and hypotheses

The total CADSS score will be also modeled with interest at 6 weeks, using MMRM with fixed, categorical effects of treatment, time (at all planned timepoints), and treatment*time interaction.

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7.2.3 Dissociative Experiences Scale (DES)

7.2.3.1 Descriptive analyses

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7.2.3.2 Statistical model, assumptions and hypotheses

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7.2.3.2.1 Supportive analysis

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7.3 Graphical presentation

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