# Clinical trial results:
# 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

## Summary

| | |
|---|---|
| EudraCT number | 2021-005992-38 |
| Trial protocol | ES PL |
| Global end of trial date | 28 November 2023 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 December 2024 |
| First version publication date | 12 December 2024 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CMIJ821B12201 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05454410 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 28 November 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of MIJ821 (versus placebo) in treatment resistant depression (TRD) after single subcutaneous (s.c.) injection.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Rescue medications were allowed and the use of these were documented in the medical records and in the electronic case report form (eCRF). Prohibited medication was administered as rescue medication if clinically warranted.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 13 March 2023 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Japan: 3 |
| Country: Number of subjects enrolled | Poland: 28 |
| Country: Number of subjects enrolled | Spain: 16 |
| Country: Number of subjects enrolled | United States: 13 |
| Worldwide total number of subjects | 60 |
| EEA total number of subjects | 44 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

| | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 60 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All inclusion and exclusion criteria were checked during screening and on Day 1, prior to randomization.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | MIJ821 10 mg |

Arm description:

Participants received a single dose of 10 mg MIJ821 administered as a subcutaneous (SC) injection on Day 1.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MIJ821 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants received a single dose of 10 mg MIJ821 administered as a subcutaneous (SC) injection on Day 1.

| | |
|---|---|
| **Arm title** | MIJ821 4 mg |

Arm description:

Participants received a single dose of 4 mg MIJ821 administered as a SC injection on Day 1.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MIJ821 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants received a single dose of 4 mg MIJ821 administered as a SC injection on Day 1.

| | |
|---|---|
| **Arm title** | MIJ821 1 mg |

Arm description:

Participants received a single dose of 1 mg MIJ821 administered as a SC injection on Day 1.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MIJ821 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants received a single dose of 1 mg MIJ821 administered as a SC injection on Day 1.

| **Arm title** | Placebo |
|---|---|

Arm description:

Participants received a single dose of 0.9% sodium chloride solution administered as a SC injection on Day 1.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants received a single dose of 0.9% sodium chloride solution administered as a SC injection on Day 1.

| **Number of subjects in period 1** | MIJ821 10 mg | MIJ821 4 mg | MIJ821 1 mg |
|---|---|---|---|
| Started | 15 | 14 | 14 |
| Completed | 15 | 14 | 13 |
| Not completed | 0 | 0 | 1 |
| Consent withdrawn by subject | - | - | 1 |

| **Number of subjects in period 1** | Placebo |
|---|---|
| Started | 17 |
| Completed | 16 |
| Not completed | 1 |
| Consent withdrawn by subject | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | MIJ821 10 mg |
| Reporting group description: | |
| Participants received a single dose of 10 mg MIJ821 administered as a subcutaneous (SC) injection on Day 1. | |
| Reporting group title | MIJ821 4 mg |
| Reporting group description: | |
| Participants received a single dose of 4 mg MIJ821 administered as a SC injection on Day 1. | |
| Reporting group title | MIJ821 1 mg |
| Reporting group description: | |
| Participants received a single dose of 1 mg MIJ821 administered as a SC injection on Day 1. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received a single dose of 0.9% sodium chloride solution administered as a SC injection on Day 1. | |

| Reporting group values | MIJ821 10 mg | MIJ821 4 mg | MIJ821 1 mg |
|---|---|---|---|
| Number of subjects | 15 | 14 | 14 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 15 | 14 | 14 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 47.8 | 43.9 | 46.9 |
| standard deviation | ± 12.36 | ± 11.29 | ± 9.73 |
| Sex/Gender, Customized<br>Units: participants | | | |
| Male | 4 | 4 | 5 |
| Female | 11 | 10 | 9 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 15 | 13 | 12 |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian / Japanese | 0 | 1 | 2 |
| Black or African American | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |

| | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 3 | 3 |
| Not Hispanic or Latino | 13 | 11 | 11 |
| Unknown or Not Reported | 0 | 0 | 0 |

| **Reporting group values** | Placebo | Total | |
|---|---|---|---|
| Number of subjects | 17 | 60 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 17 | 60 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 47.1 | | |
| standard deviation | ± 12.05 | - | |
| Sex/Gender, Customized<br>Units: participants | | | |
| Male | 10 | 23 | |
| Female | 7 | 37 | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 17 | 57 | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian / Japanese | 0 | 3 | |
| Black or African American | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 0 | 8 | |
| Not Hispanic or Latino | 17 | 52 | |
| Unknown or Not Reported | 0 | 0 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | MIJ821 10 mg |
| Reporting group description: | |
| Participants received a single dose of 10 mg MIJ821 administered as a subcutaneous (SC) injection on Day 1. | |
| Reporting group title | MIJ821 4 mg |
| Reporting group description: | |
| Participants received a single dose of 4 mg MIJ821 administered as a SC injection on Day 1. | |
| Reporting group title | MIJ821 1 mg |
| Reporting group description: | |
| Participants received a single dose of 1 mg MIJ821 administered as a SC injection on Day 1. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received a single dose of 0.9% sodium chloride solution administered as a SC injection on Day 1. | |
| Subject analysis set title | Overall |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Pooled for all participants | |

### Primary: Change from Baseline in Montgomery Asberg Depression Rating Scale (MADRS) Total Score 24 Hours (Day 2) after Injection

| | |
|---|---|
| End point title | Change from Baseline in Montgomery Asberg Depression Rating Scale (MADRS) Total Score 24 Hours (Day 2) after Injection |
| End point description: | |
| The Montgomery Åsberg Depression Rating Scale (MADRS, SIGMA version), is a clinician rated scale designed to measure depression severity and detects changes due to antidepressant treatment. The test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 0 - 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts and suicidal thoughts. The MADRS scores were collected electronically by qualified personnel. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and 24 hours after SC injection | |

| End point values | MIJ821 10 mg | MIJ821 4 mg | MIJ821 1 mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 14 | 14 | 17 |
| Units: Scores on a Scale | | | | |
| least squares mean (standard error) | -14.1 (± 1.95) | -11.4 (± 2.04) | -8.4 (± 2.02) | -8.9 (± 1.82) |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | MIJ821 10 mg v Placebo |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -5.2 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -9.6 |
| upper limit | -0.7 |

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | MIJ821 4 mg v Placebo |
| Number of subjects included in analysis | 31 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2.5 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -7 |
| upper limit | 2.1 |

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|
| Comparison groups | MIJ821 1 mg v Placebo |
| Number of subjects included in analysis | 31 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | ANCOVA |
| Parameter estimate | Median difference (net) |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | 5.1 |

## Secondary: Percentage of Participants with Treatment-Emergent Adverse Events

## (TEAEs), including Adverse Events of Special Interest (AESIs)

| End point title | Percentage of Participants with Treatment-Emergent Adverse Events (TEAEs), including Adverse Events of Special Interest (AESIs) |
|---|---|

End point description:

A TEAE was defined as an adverse event starting or worsening after the administration of study medication and up to the end of study visit. The following events were considered AESIs:

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

| End point type | Secondary |
|---|---|

End point timeframe:

From Day 1 after SC injection to end of study, up to 29 Days

| **End point values** | MIJ821 10 mg | MIJ821 4 mg | MIJ821 1 mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 14 | 14 | 17 |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| With at least one AE | 66.67 | 42.86 | 28.57 | 41.18 |
| With at least one AESI | 60 | 35.71 | 14.29 | 17.65 |
| Blood pressure increased | 0 | 7.14 | 7.14 | 0 |
| Dissociation | 33.33 | 14.29 | 0 | 11.76 |
| Derealization | 6.67 | 0 | 0 | 0 |
| Vision blurred | 0 | 0 | 7.14 | 0 |
| Amnesia | 6.67 | 0 | 0 | 0 |
| Somnolence | 26.67 | 7.14 | 0 | 5.88 |
| Sedation | 6.67 | 7.14 | 0 | 0 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics (PK) of MIJ821 in Plasma for Area Under the Curve from the Time of Dosing to the Time of the Last Measurable Concentration (AUClast)

| End point title | Pharmacokinetics (PK) of MIJ821 in Plasma for Area Under the Curve from the Time of Dosing to the Time of the Last Measurable Concentration (AUClast)[1] |
|---|---|

End point description:

Blood samples were collected at the indicated time points for PK analysis. AUClast was defined as the area under the curve from time zero to the last measurable concentration sampling time (tlast).

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, 0.17 hour, 0.33 hour, 0.5 hour, 0.75 hour, 1, 1.5, 2, 4 and 24 hours post injection

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic parameters were only analyzed in the MIJ821 arms.

| **End point values** | MIJ821 10 mg | MIJ821 4 mg | MIJ821 1 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 15 | 13 | 13 | |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 231 (± 33.5) | 89.5 (± 45.7) | 5.92 (± 85.1) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: PK of MIJ821 in Plasma for Maximum Serum Concentration (Cmax)

| End point title | PK of MIJ821 in Plasma for Maximum Serum Concentration (Cmax)[2] |
|---|---|

End point description:

Blood samples were collected at the indicated time points for PK analysis. Cmax was defined as the maximum (peak) observed plasma drug concentration after single dose administration.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, 0.17 hour, 0.33 hour, 0.5 hour, 0.75 hour, 1, 1.5, 2, 4 and 24 hours post injection

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic parameters were only analyzed in the MIJ821 arms.

| **End point values** | MIJ821 10 mg | MIJ821 4 mg | MIJ821 1 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 15 | 13 | 13 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 42.7 (± 37.2) | 17.5 (± 46.7) | 2.32 (± 55.4) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: PK of MIJ821 in Plasma for Time to Maximum Drug Concentration (Tmax)

| End point title | PK of MIJ821 in Plasma for Time to Maximum Drug Concentration (Tmax)[3] |
|---|---|

End point description:

Blood samples were collected at the indicated time points for PK analysis. Tmax was defined as the time to reach maximum (peak) plasma drug concentration after single dose administration (time).

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, 0.17 hour, 0.33 hour, 0.5 hour, 0.75 hour, 1, 1.5, 2, 4 and 24 hours post injection

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic parameters were only analyzed in the MIJ821 arms.

| **End point values** | MIJ821 10 mg | MIJ821 4 mg | MIJ821 1 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 15 | 14 | 14 | |
| Units: hour (h) | | | | |
| median (full range (min-max)) | 0.750 (0.333 to 2.00) | 0.500 (0.150 to 1.00) | 0.500 (0.167 to 0.783) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the MADRS Total Scores at Day 8, 15, 22 and 29 Visits

| End point title | Change from Baseline in the MADRS Total Scores at Day 8, 15, 22 and 29 Visits |
|---|---|

End point description:

The MADRS (SIGMA version), is a clinician rated scale designed to measure depression severity and detects changes due to antidepressant treatment. The test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 0 - 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts and suicidal thoughts. The MADRS scores were collected electronically by qualified personnel.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Days 8, 15, 22 and 29

| **End point values** | MIJ821 10 mg | MIJ821 4 mg | MIJ821 1 mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 14 | 14 | 17 |
| Units: Scores on a Scale | | | | |
| least squares mean (standard error) | | | | |
| Change from Baseline (Day 8) n=15,14,14,17 | -15.3 (± 2.0) | -9.9 (± 2.1) | -8.2 (± 2.0) | -7.4 (± 1.8) |
| Change from Baseline (Day 15) n=14,13,14,17 | -14.0 (± 2.2) | -8.5 (± 2.2) | -11.0 (± 2.2) | -7.7 (± 2.0) |
| Change from Baseline (Day 22) n=14,14,13,17 | -14.9 (± 2.2) | -10.7 (± 2.3) | -9.7 (± 2.3) | -7.0 (± 2.0) |
| Change from Baseline (Day 29) n=14,14,13,16 | -14.9 (± 2.3) | -12.7 (± 2.4) | -10.7 (± 2.4) | -7.0 (± 2.1) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Dose-response (DR) Relationship of MIJ821 with Respect to Change from Baseline in MADRS Total Score at 24 Hours after Single SC injection

| End point title | Dose-response (DR) Relationship of MIJ821 with Respect to Change from Baseline in MADRS Total Score at 24 Hours after Single SC injection |
|---|---|

End point description:

The multiple comparison procedure - modelling (MCP-Mod) approach was an integrated approach used to investigate DR relationships, while confirming efficacy of the test product based on hypothesis testing. A set of candidate models was tested using Multiple Comparison Procedures (MCP) that preserve the family-wise error rate (FWER). Efficacy via DR was established when at least one of the model tests was significant.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to 24 Hours

| End point values | MIJ821 10 mg | MIJ821 4 mg | MIJ821 1 mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 14 | 14 | 17 |
| Units: Scores on a Scale | | | | |
| least squares mean (standard error) | -14.1 (± 1.95) | -11.4 (± 2.04) | -8.4 (± 2.02) | -8.9 (± 1.82) |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

MCP-Mod was used to check if there was a DR relationship between the change from baseline to 24 hours in MADRS total score and the doses received. The Least squares means under the primary estimand were used to test the null hypothesis of a flat DR relationship at a one-sided significance level of 5% against the alternative hypothesis of a non-flat DR curve. Six candidate DR curves were used to derive the optimal model contrasts for the multiple contrast tests. A monotone DR was assumed.

| Comparison groups | MIJ821 10 mg v MIJ821 4 mg v MIJ821 1 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0242 [4] |
| Method | Multiple contrast test |

Notes:

[4] - P-values were adjusted for multiple comparisons.

## Secondary: Exposure-response Relationship of MIJ821 with Respect to Change from Baseline in MADRS Total Score

| End point title | Exposure-response Relationship of MIJ821 with Respect to Change from Baseline in MADRS Total Score |
|---|---|

End point description:

The exposure-response (ER) relationship was investigated considering PK exposure parameters (AUClast and Cmax) and the change from baseline MADRS score derived at 4 h and 24 h after injection and Day 8, Day 15, Day 22 and Day 29 during the follow-up.
The emax model or sigmoid emax model were planned to be fitted for the change from baseline at each follow up visit and the PK exposure parameters, Cmax and AUClast. If the model converges, parameters estimated from the Sigmoid emax model are: the placebo effect E0, EC50, Emax and the hill parameter.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Day 2, 15, 22 and 29

| **End point values** | Overall | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 41 | | | |
| Units: parameter estimate from model | | | | |
| ER Relationship Cmax: placebo effect E0 | 999 | | | |
| ER Relationship Cmax: EC50 | 999 | | | |
| ER Relationship Cmax: Emax | 999 | | | |
| ER Relationship Cmax: hill parameter | 999 | | | |
| ER Relationship AUClast: placebo effect E0 | 999 | | | |
| ER Relationship AUClast: EC50 | 999 | | | |
| ER Relationship AUClast: Emax | 999 | | | |
| ER Relationship AUClast: hill parameter | 999 | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment, up to a maximum duration of 29 days.

Adverse event reporting additional description:

The Safety Analysis Set included all participants who received any study drug. Participants were analyzed according to the study treatment received.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | MIJ821 10mg |

Reporting group description:

Participants received a single dose of 10 mg MIJ821 administered as a subcutaneous (SC) injection on Day 1.

| | |
|---|---|
| Reporting group title | MIJ821 4mg |

Reporting group description:

Participants received a single dose of 4 mg MIJ821 administered as a SC injection on Day 1.

| | |
|---|---|
| Reporting group title | MIJ821 1mg |

Reporting group description:

Participants received a single dose of 1 mg MIJ821 administered as a SC injection on Day 1.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Participants received a single dose of 0.9% sodium chloride solution administered as a SC injection on Day 1.

| | |
|---|---|
| Reporting group title | All MIJ821 |

Reporting group description:

All MIJ821 Dosages

| | |
|---|---|
| Reporting group title | All Subjects |

Reporting group description:

All Subjects included in the Safety Analysis Set

| Serious adverse events | MIJ821 10mg | MIJ821 4mg | MIJ821 1mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Placebo | All MIJ821 | All Subjects |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 43 (0.00%) | 0 / 60 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| number of deaths resulting from adverse events | 0 | 0 | 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | MIJ821 10mg | MIJ821 4mg | MIJ821 1mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 15 (66.67%) | 6 / 14 (42.86%) | 4 / 14 (28.57%) |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 14 (7.14%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Heart rate increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Sedation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 14 (7.14%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Headache | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 0 / 14 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 3 | 0 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Amnesia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 4 / 15 (26.67%) | 1 / 14 (7.14%) | 0 / 14 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Tension headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site erythema | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Dissociation | | | |
| subjects affected / exposed | 5 / 15 (33.33%) | 2 / 14 (14.29%) | 0 / 14 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Derealisation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 14 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 14 (7.14%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| **Non-serious adverse events** | Placebo | All MIJ821 | All Subjects |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 17 (41.18%) | 20 / 43 (46.51%) | 27 / 60 (45.00%) |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 43 (4.65%) | 2 / 60 (3.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Heart rate increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 43 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Nervous system disorders | | | |
| Sedation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 43 (4.65%) | 2 / 60 (3.33%) |
| occurrences (all) | 0 | 2 | 2 |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 4 / 43 (9.30%) | 7 / 60 (11.67%) |
| occurrences (all) | 4 | 4 | 8 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 43 (2.33%) | 2 / 60 (3.33%) |
| occurrences (all) | 1 | 1 | 2 |
| Amnesia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 5 / 43 (11.63%) | 6 / 60 (10.00%) |
| occurrences (all) | 1 | 5 | 6 |
| Tension headache | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 43 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 43 (6.98%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 3 | 3 |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 43 (0.00%) | 2 / 60 (3.33%) |
| occurrences (all) | 2 | 0 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 43 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 43 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Dissociation | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 7 / 43 (16.28%) | 9 / 60 (15.00%) |
| occurrences (all) | 2 | 7 | 9 |
| Derealisation | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Depression | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Infections and infestations | | | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 43 (2.33%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 31 May 2022 | Amendment 01 includes the following: The purpose of this protocol amendment was to clarify that the End of-Study visit (Day 29) was the last study visit for ensuring safety follow-up and thus a safety follow-up call at Day 31 was not required while taking into consideration the pharmacokinetic profile of MIJ821 (five times the apparent terminal elimination half-life of MIJ821).<br><br>The protocol was amended to clarify that in case of extended safety monitoring for adverse events on Day 1, between 4 hours and 24 hours post-dose, additional safety tests or measures were required, including but not limited to, unscheduled PK samples.<br><br>The recall periods for the MADRS and the Clinical Global Impression - Severity (CGI-S) scale were added in order to adequately assess efficacy at the 4 hour-time point on Day 1. In addition, the recall period of the MADRS used at screening had specified: “Last 7 days with euthymic baseline”. The recall period of the Clinician-Administered Dissociative States Scale (CADSS) was also added. The recall period of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the first study visit was updated to reflect that this version assessed suicidal ideation and suicidal behavior during the participant's last one year and during a predefined period of one month. |
| 04 November 2022 | Amendment 02 includes the following: The purpose of this protocol amendment was to replace the Mini International Neuropsychiatric Interview (M.I.N.I), used at screening to assess whether the diagnostic criteria was met, with an equivalent validated instrument: the Structured Clinical Interview for DSM-5 Disorders (SCID-5). The M.I.N.I was not to be used in this trial due to difficulties related to copyright license agreement's activities, which were not to be overcome in a timely manner. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results. |

Notes: