Clinical trial results:
A multi-center, randomized, subject and investigatorblinded, placebo-controlled, active comparator, parallelgroup proof of concept study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of MIJ821 in patients with treatment-resistant depression

Summary

EudraCT number	2018-003002-12
Trial protocol	ES
Global end of trial date	23 March 2020

Results information

Result version number	v2
This version publication date	23 June 2021
First version publication date	17 March 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CMIJ821X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03756129
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	23 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess efficacy of MIJ821 in treatment-resistant depression.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 February 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	70
EEA total number of subjects	16

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)	69
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall, 72 subjects were randomized in this study, and 2 of them discontinued from study before receiving any study treatment. All the 70 treated subjects were included in both efficacy and safety analyses. Fifty subjects treated with MIJ821 or ketamine were included in the pharmacokinetic analysis.

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	Investigator, Monitor, Carer, Data analyst, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	MIJ821 0.16 mg/kg weekly

Arm description:

MIJ821 0.16 mg/kg weekly

Arm type	Experimental
Investigational medicinal product name	MIJ821
Investigational medicinal product code	MIJ821
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

MIJ821 fixed dose of 0.16 mg/kg, one infusion per week from Day 1 to Day 36

Arm title	MIJ821 0.16 mg/kg biweekly

Arm description:

MIJ821 0.16 mg/kg biweekly

Arm type	Experimental
Investigational medicinal product name	MIJ821
Investigational medicinal product code	MIJ821
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

MIJ821 fixed dose of 0.16 mg/kg one infusion biweekly on Day 1, Day 15, and Day 29, placebo on Day 8, Day 22 and Day 36

Arm title	MIJ821 0.32 mg/kg weekly

Arm description:

MIJ821 0.32 mg/kg weekly

Arm type	Experimental

Investigational medicinal product name	MIJ821
Investigational medicinal product code	MIJ821
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

MIJ821 fixed dose of 0.32 mg/kg, one infusion per week from Day 1 to Day 36

Arm title	MIJ821 0.32 mg/kg biweekly

Arm description:

MIJ821 0.32 mg/kg biweekly

Arm type	Experimental
Investigational medicinal product name	MIJ821
Investigational medicinal product code	MIJ821
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

MIJ821 fixed dose of 0.32 mg/kg one infusion biweekly on Day 1, Day 15, and Day 29, placebo on Day 8, Day 22 and Day 36

Arm title	Ketamine 0.5 mg/kg weekly

Arm description:

Ketamine 0.5 mg/kg weekly

Arm type	Active comparator
Investigational medicinal product name	Ketamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ketamine fixed dose of 0.5 mg/kg, limiting dose at 40 mg/infusion for subjects over 80 kg, one infusion per week from Day 1 to Day 36 (absence of the ketamine arm in the US)

Arm title	Placebo weekly

Arm description:

Placebo weekly

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo, one infusion per week from Day 1 to Day 36

Number of subjects in period 1	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly
Started	11	10	10
Completed	8	8	7
Not completed	3	2	3
Consent withdrawn by subject	2	1	3
Physician decision	-	-	-
Adverse event, non-fatal	1	1	-
Lost to follow-up	-	-	-

Number of subjects in period 1	MIJ821 0.32 mg/kg biweekly	Ketamine 0.5 mg/kg weekly	Placebo weekly
Started	9	10	20
Completed	6	9	15
Not completed	3	1	5
Consent withdrawn by subject	1	1	3
Physician decision	-	-	1
Adverse event, non-fatal	2	-	-
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	MIJ821 0.16 mg/kg weekly
Reporting group description: MIJ821 0.16 mg/kg weekly	
Reporting group title	MIJ821 0.16 mg/kg biweekly
Reporting group description: MIJ821 0.16 mg/kg biweekly	
Reporting group title	MIJ821 0.32 mg/kg weekly
Reporting group description: MIJ821 0.32 mg/kg weekly	
Reporting group title	MIJ821 0.32 mg/kg biweekly
Reporting group description: MIJ821 0.32 mg/kg biweekly	
Reporting group title	Ketamine 0.5 mg/kg weekly
Reporting group description: Ketamine 0.5 mg/kg weekly	
Reporting group title	Placebo weekly
Reporting group description: Placebo weekly	

Reporting group values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly
Number of subjects	11	10	10
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	11	9	10
>=65 years	0	1	0
Age Continuous Units: Years			
arithmetic mean	48.6	53.7	42.9
standard deviation	± 11.70	± 9.33	± 14.47
Sex: Female, Male Units: Participants			
Female	2	5	6
Male	9	5	4
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	4	4
White	8	6	6
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	MIJ821 0.32 mg/kg	Ketamine 0.5 mg/kg	Placebo weekly

	biweekly	weekly	
Number of subjects	9	10	20
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	9	10	20
>=65 years	0	0	0
Age Continuous Units: Years			
arithmetic mean	46.6	52.3	44.8
standard deviation	± 11.83	± 6.96	± 10.69
Sex: Female, Male Units: Participants			
Female	6	7	9
Male	3	3	11
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	0	10
White	1	9	9
More than one race	0	1	0
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	70		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	69		
>=65 years	1		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	35		
Male	35		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	29		
White	39		
More than one race	1		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	MIJ821 0.16 mg/kg weekly
Reporting group description: MIJ821 0.16 mg/kg weekly	
Reporting group title	MIJ821 0.16 mg/kg biweekly
Reporting group description: MIJ821 0.16 mg/kg biweekly	
Reporting group title	MIJ821 0.32 mg/kg weekly
Reporting group description: MIJ821 0.32 mg/kg weekly	
Reporting group title	MIJ821 0.32 mg/kg biweekly
Reporting group description: MIJ821 0.32 mg/kg biweekly	
Reporting group title	Ketamine 0.5 mg/kg weekly
Reporting group description: Ketamine 0.5 mg/kg weekly	
Reporting group title	Placebo weekly
Reporting group description: Placebo weekly	
Subject analysis set title	Pooled MIJ821 0.16 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: Pooled MIJ821 0.16 mg/kg	
Subject analysis set title	Pooled MIJ821 0.32 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: Pooled MIJ821 0.32 mg/kg	
Subject analysis set title	Pooled MIJ821 0.16 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: Pooled MIJ821 0.16 mg/kg	
Subject analysis set title	Pooled MIJ821 0.32 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: Pooled MIJ821 0.32 mg/kg	
Subject analysis set title	Pooled MIJ821 0.16 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: Pooled MIJ821 0.16 mg/kg	
Subject analysis set title	Pooled MIJ821 0.32 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: Pooled MIJ821 0.32 mg/kg	
Subject analysis set title	Koukopoulos
Subject analysis set type	Full analysis
Subject analysis set description: Koukopoulos Mixed Depression Rating Scale	
Subject analysis set title	Angst

Subject analysis set type	Full analysis
Subject analysis set description: Mixed depression checklist, created by Angst	
Subject analysis set title	Ghaemi
Subject analysis set type	Full analysis
Subject analysis set description: Melancholia checklist, created by Ghaemi	
Subject analysis set title	Ketamine 0.5 mg/kg weekly
Subject analysis set type	Full analysis
Subject analysis set description: Ketamine 0.5 mg/kg weekly	
Subject analysis set title	Placebo weekly
Subject analysis set type	Full analysis
Subject analysis set description: Placebo weekly	

Primary: Change from baseline in the total score of the Montgomery Asberg Depression Rating Scale (MADRS) at 24 hrs

End point title	Change from baseline in the total score of the Montgomery Asberg Depression Rating Scale (MADRS) at 24 hrs
End point description: Efficacy. To assess change from baseline in the total MADRS score. The efficacy of MIJ821 in treatment-resistant depression will be compared to the placebo after single dose administration. MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment: the test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition.	
End point type	Primary
End point timeframe: Baseline, and at 24 hours	

End point values	Pooled MIJ821 0.16 mg/kg	Pooled MIJ821 0.32 mg/kg	Ketamine 0.5 mg/kg weekly	Placebo weekly
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	19	10	20
Units: Scores on a Scale				
least squares mean (standard error)	-15.51 (± 1.9)	-12.98 (± 1.9)	-12.94 (± 2.7)	-7.27 (± 1.9)

Statistical analyses

Statistical analysis title	Comparison of adjusted arithmetic mean
Statistical analysis description: Comparison of adjusted arithmetic mean: Mean Difference: "Pooled MIJ821 0.16 mg/kg" minus "placebo". The MIJ821 treatment arms vs placebo are primary.	
Comparison groups	Pooled MIJ821 0.16 mg/kg v Placebo weekly

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0013
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-8.25
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-11.67
upper limit	-4.83

Statistical analysis title	Comparison of adjusted arithmetic mean
Statistical analysis description:	
Comparison of adjusted arithmetic mean: Mean Difference: "Pooled MIJ821 0.32 mg/kg" minus "placebo". The MIJ821 treatment arms vs placebo are primary.	
Comparison groups	Pooled MIJ821 0.32 mg/kg v Placebo weekly
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0196
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.71
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-9.22
upper limit	-2.2

Secondary: Change from baseline in the total score of the Montgomery Asberg Depression Rating Scale (MADRS) at 48 hrs

End point title	Change from baseline in the total score of the Montgomery Asberg Depression Rating Scale (MADRS) at 48 hrs
End point description:	
Efficacy. To assess change from baseline in the total MADRS score. The efficacy of MIJ821 in treatment-resistant depression will be compared to the placebo after single dose administration. MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment: the test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition.	
End point type	Secondary
End point timeframe:	
Baseline, and at 48 hours	

End point values	Pooled MIJ821 0.16 mg/kg	Pooled MIJ821 0.32 mg/kg	Ketamine 0.5 mg/kg weekly	Placebo weekly
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	16	4	19
Units: Scores on a Scale				
least squares mean (standard error)	-14.94 (± 2.2)	-15.25 (± 2.4)	-18.89 (± 4.8)	-7.88 (± 2.2)

Statistical analyses

Statistical analysis title	Comparison of adjusted arithmetic mean
Statistical analysis description:	
Comparison of adjusted arithmetic mean: Mean Difference: "Pooled MIJ821 0.16 mg/kg" minus "placebo".	
Comparison groups	Pooled MIJ821 0.16 mg/kg v Placebo weekly
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7.06
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-11.06
upper limit	-3.06

Statistical analysis title	Comparison of adjusted arithmetic mean
Statistical analysis description:	
Comparison of adjusted arithmetic mean: Mean Difference: "Pooled MIJ821 0.32 mg/kg" minus "placebo".	
Comparison groups	Pooled MIJ821 0.32 mg/kg v Placebo weekly
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0133
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-7.37
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-11.57
upper limit	-3.18

Secondary: Change from baseline in the total score of the Montgomery Asberg Depression Rating Scale (MADRS) at week 6

End point title	Change from baseline in the total score of the Montgomery Asberg Depression Rating Scale (MADRS) at week 6

End point description:

Efficacy. To assess change from baseline in the total MADRS score. The efficacy of MIJ821 in treatment-resistant depression will be compared to the placebo after single dose administration. MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment: the test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition.

End point type	Secondary

End point timeframe:

Baseline, and at Week 6

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
least squares mean (standard error)	-12.71 (± 3.4)	-14.08 (± 3.4)	-13.04 (± 3.5)	-10.68 (± 3.9)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
least squares mean (standard error)	-12.86 (± 3.3)	-7.62 (± 2.3)		

Statistical analyses

Statistical analysis title	Comparison of adjusted arithmetic mean

Statistical analysis description:

Comparison of adjusted arithmetic mean: Mean Difference: “MIJ821 0.16 mg/kg weekly” minus “placebo”.

Comparison groups	MIJ821 0.16 mg/kg weekly v Placebo weekly
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1082
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.09

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-10.37
upper limit	0.19

Statistical analysis title	Comparison of adjusted arithmetic mean
Statistical analysis description:	
Comparison of adjusted arithmetic mean: Mean Difference: "MIJ821 0.32 mg/kg weekly" minus "placebo".	
Comparison groups	MIJ821 0.32 mg/kg weekly v Placebo weekly
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0993
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.42
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-10.83
upper limit	-0.02

Statistical analysis title	Comparison of adjusted arithmetic mean
Statistical analysis description:	
Comparison of adjusted arithmetic mean: Mean Difference: "MIJ821 0.16 mg/kg biweekly" minus "placebo".	
Comparison groups	MIJ821 0.16 mg/kg biweekly v Placebo weekly
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0598
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-6.46
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-11.78
upper limit	-1.15

Statistical analysis title	Comparison of adjusted arithmetic mean

Statistical analysis description:

Comparison of adjusted arithmetic mean: Mean Difference: “MIJ821 0.32 mg/kg biweekly” minus “placebo”.

Comparison groups	MIJ821 0.32 mg/kg biweekly v Placebo weekly
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2491
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.06
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-8.86
upper limit	2.74

Secondary: Change from baseline in the Young Mania Rating Scale

End point title	Change from baseline in the Young Mania Rating Scale

End point description:

To assess risk of mania induction. The Young Mania Rating Scale has 11 items and is based on the patient's subjective report of his/her clinical condition over the previous 48 hours. There are 4 items that are scored from 0 to 8 (irritability, speech, thought content, and disruptive/aggressive behavior) and the remaining items are scored from 0 to 4. Higher scores indicate more severe mania.

The total clinical score was calculated as the summation of the individual subscale scores. The maximum for the total YMRS score is 60. The range is 0 to 60 with the higher score indicating more severe symptoms.

End point type	Secondary

End point timeframe:

Baseline, 24 hours, and 6 weeks (day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
least squares mean (standard error)				
Adjusted mean change from b/l to 24 hrs	-1.41 (± 0.5)	-1.07 (± 0.5)	-1.66 (± 0.5)	-0.81 (± 0.5)
Adjusted mean change from b/l to day 43	-1.28 (± 0.6)	-2.13 (± 0.7)	-0.65 (± 0.7)	-1.55 (± 0.7)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
least squares mean (standard error)				
Adjusted mean change from b/l to 24 hrs	-1.56 (± 0.5)	-0.72 (± 0.3)		
Adjusted mean change from b/l to day 43	-1.80 (± 0.7)	-0.92 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bech-Rafaelsen melancholia scale

End point title	Bech-Rafaelsen melancholia scale

End point description:

To assess efficacy in the melancholic subtype of depression. Depression scales are used primarily to measure changes, for example, to evaluate the efficacy of treatment with antidepressants. The Bech-Rafaelsen Melancholia Scale (BRMS) is a frequently used clinician rating scale to assess the severity of depression over the past 3 days. Each of the 11 BRMS items is operationally defined on a five-point scale (0-4); hence, the total score ranges from 0 to 44, higher scores indicating greater severity of depression.

End point type	Secondary

End point timeframe:

24 hours, 48 hours and 6 weeks (Day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Change at 24 hrs	-11.9 (± 5.941)	-9.5 (± 4.625)	-7.9 (± 6.903)	-8.1 (± 4.612)
Change at 48 hrs	-9.9 (± 5.326)	-8.0 (± 5.185)	-7.6 (± 8.383)	-8.0 (± 5.508)
Change at day 43	-8.6 (± 6.589)	-8.6 (± 5.423)	-7.6 (± 10.013)	-6.0 (± 9.338)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Change at 24 hrs	-7.7 (± 5.766)	-6.0 (± 5.262)		
Change at 48 hrs	-12.5 (± 7.853)	-6.7 (± 6.659)		

Change at day 43	-8.9 (± 8.343)	-6.9 (± 5.988)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK properties of MIJ821 in plasma - Cmax (ng/mL)

End point title	PK properties of MIJ821 in plasma - Cmax (ng/mL)

End point description:

To assess MIJ821 pharmacokinetics in plasma described by Cmax

End point type	Secondary

End point timeframe:

Day 1

End point values	Pooled MIJ821 0.16 mg/kg	Pooled MIJ821 0.32 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	11		
Units: ng/mL				
arithmetic mean (standard deviation)	99.5 (± 47.8)	149 (± 63.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK properties of MIJ821 in plasma - Tmax (ng/mL)

End point title	PK properties of MIJ821 in plasma - Tmax (ng/mL)

End point description:

To assess MIJ821 pharmacokinetics in plasma described by Tmax

End point type	Secondary

End point timeframe:

Day 1

End point values	Pooled MIJ821 0.16 mg/kg	Pooled MIJ821 0.32 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	11		
Units: hour				
median (full range (min-max))	0.683 (0.650 to 0.700)	0.667 (0.667 to 0.700)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK properties of MIJ821 in plasma - AUClast (h*ng/mL)

End point title	PK properties of MIJ821 in plasma - AUClast (h*ng/mL)

End point description:

To assess MIJ821 pharmacokinetics in plasma described by AUClast (h*ng/mL)

End point type	Secondary

End point timeframe:

Day 1

End point values	Pooled MIJ821 0.16 mg/kg	Pooled MIJ821 0.32 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	11		
Units: h*ng/mL				
arithmetic mean (standard deviation)	496 (± 239)	738 (± 302)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK properties of MIJ821 in plasma - AUC0-24h (h*ng/mL)

End point title	PK properties of MIJ821 in plasma - AUC0-24h (h*ng/mL)

End point description:

To assess MIJ821 pharmacokinetics in plasma described by AUC0-24h (h*ng/mL)

End point type	Secondary

End point timeframe:

Day 1

End point values	Pooled MIJ821 0.16 mg/kg	Pooled MIJ821 0.32 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	11		
Units: h*ng/mL				
arithmetic mean (standard deviation)	462 (± 232)	713 (± 275)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the CORE Melancholia Total Scale

End point title	Change from baseline in the CORE Melancholia Total Scale

End point description:

To assess efficacy in melancholic subtype of depression. This scale is an 18 item scale, with a 6 item component capturing cognitive impairment and two motoric scales capturing psychomotor retardation (7 items) and psychomotor agitation (5 items). A cut-off score of 8 or more has been shown to ifferentiate melancholic from non-melancholic depression, with higher scores representing a greater probability of melancholic depression. (Parker and McCraw 2017).

The total clinical score was calculated as the summation of the individual subscale scores. The maximum for the total CORE Melancholia score is 54. The range is 0 to 54 with the higher score indicating more severe symptoms.

End point type	Secondary

End point timeframe:

Baseline, 24 hours, 48 hrs, and 6 weeks (day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
least squares mean (standard error)				
Adjusted mean change from b/l to 24 hrs	-4.76 (± 2.9)	-3.64 (± 3.6)	-3.93 (± 3.0)	1.38 (± 3.5)
Adjusted mean change from b/l to 48 hrs	-5.77 (± 3.9)	-2.82 (± 3.7)	-5.92 (± 3.2)	1.62 (± 4.0)
Adjusted mean change from b/l to day 43	-5.79 (± 3.4)	-4.82 (± 4.4)	-7.24 (± 3.5)	-6.49 (± 4.3)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
least squares mean (standard error)				

Adjusted mean change from b/l to 24 hrs	-5.07 (± 2.0)	-3.61 (± 2.0)		
Adjusted mean change from b/l to 48 hrs	-6.68 (± 2.6)	-5.06 (± 1.9)		
Adjusted mean change from b/l to day 43	-9.01 (± 2.1)	-5.21 (± 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Adverse Events

End point title	Summary of Adverse Events

End point description:

Summary of Adverse Events

End point type	Secondary

End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 post treatment, up to a maximum duration of 66 days.

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Participants				
AEs, subjects with AEs	7	6	7	6
Study drug-related AEs	5	5	7	5
SAEs	0	1	0	3
AEs leading to disc.of study treatment	1	0	0	2
Study drug-related AEs leading to disc.	0	0	0	0

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Participants				
AEs, subjects with AEs	6	7		
Study drug-related AEs	6	5		
SAEs	0	1		
AEs leading to disc.of study treatment	0	1		
Study drug-related AEs leading to disc.	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinician-Administered Dissociative States Scale

End point title	Clinician-Administered Dissociative States Scale

End point description:

To assess safety and tolerability, especially dissociative side effects. The Clinical-Administered Dissociative States Scale (CADSS) is a questionnaire that assesses dissociative effects. Each item is scored from 0 to 4 and individual scores are to be summed to obtain a total score ranging from a minimum of 0 to a maximum of 80. Higher scores represent a more severe condition.

End point type	Secondary

End point timeframe:

Change from baseline at 24 hours, 48 hours, and 6 weeks (Day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Change at 24 hrs	1.09 (± 5.262)	1.10 (± 2.726)	2.10 (± 3.414)	3.00 (± 3.703)
Change at 48 hrs	-0.22 (± 0.667)	0.50 (± 2.369)	4.44 (± 10.394)	3.14 (± 3.976)
Change at day 43	0.00 (± 1.927)	0.00 (± 0.00)	0.38 (± 1.061)	1.00 (± 2.449)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Change at 24 hrs	-0.50 (± 0.707)	-0.25 (± 0.716)		
Change at 48 hrs	0.00 (± 0.00)	-0.16 (± 0.375)		
Change at day 43	0.00 (± 1.118)	-0.18 (± 0.636)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Dissociative Experiences Total Score

End point title	Change from baseline in the Dissociative Experiences Total Score

End point description:

The Dissociative Experiences Scale (DES) consists of twenty-eight questions about experiences the subject has experienced in his/her daily life. The subject determines to what degree he/she has been facing the situation by selecting a percentage from 0% (never) to 100% (always), with 10% increments in between. Higher scores mean higher severity.

End point type	Secondary

End point timeframe:

Baseline, 24 hours, 48 hrs, and 6 weeks (day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
least squares mean (standard error)				
Adjusted mean change from b/l to 24 hrs	1.82 (± 1.0)	2.00 (± 1.1)	1.20 (± 1.1)	7.22 (± 1.1)
Adjusted mean change from b/l to 48 hrs	1.80 (± 1.1)	2.30 (± 1.1)	1.89 (± 1.1)	3.46 (± 1.2)
Adjusted mean change from b/l to day 43	1.38 (± 1.1)	1.61 (± 1.1)	1.02 (± 1.1)	0.24 (± 1.3)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
least squares mean (standard error)				
Adjusted mean change from b/l to 24 hrs	2.10 (± 1.1)	2.50 (± 0.8)		
Adjusted mean change from b/l to 48 hrs	1.89 (± 1.4)	2.43 (± 0.8)		
Adjusted mean change from b/l to day 43	1.86 (± 1.1)	2.63 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sheehan Suicidality Tracking Scale - (SSTS)

End point title	Sheehan Suicidality Tracking Scale - (SSTS)

End point description:

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). Higher scores represent a more severe condition.

End point type	Secondary

End point timeframe:

Change from baseline at 24 hours, 48 hours, and 6 weeks (Day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Suicidal behavior score -Change at 24 hrs	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	0.11 (± 0.333)
Suicidal behavior score -Change at 48 hrs	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)
Suicidal behavior score- Change at day 43	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)
Suicidal ideation score - Change at 24 hrs	-0.45 (± 0.820)	-0.50 (± 0.850)	-0.30 (± 0.675)	0.11 (± 1.269)
Suicidal ideation score - Change at 48 hrs	-0.22 (± 0.667)	-0.50 (± 0.850)	-0.33 (± 0.707)	-0.43 (± 0.787)
Suicidal ideation score - Change at day 43	-0.38 (± 0.744)	-0.13 (± 0.354)	-0.13 (± 1.126)	0.00 (± 1.265)
SSTS total score - Change at 24 hrs	-0.45 (± 0.820)	-0.50 (± 0.850)	-0.30 (± 0.675)	0.11 (± 1.764)
SSTS total score Change at 48 hrs	-0.22 (± 0.667)	-0.50 (± 0.850)	-0.33 (± 0.707)	-0.57 (± 1.134)
SSTS total score - Change at Day 43	-0.38 (± 0.744)	-0.13 (± 0.354)	-0.13 (± 1.126)	-0.17 (± 1.602)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Suicidal behavior score -Change at 24 hrs	-0.10 (± 0.316)	0.00 (± 0.00)		
Suicidal behavior score -Change at 48 hrs	0.00 (± 0.00)	0.00 (± 0.00)		
Suicidal behavior score- Change at day 43	-0.11 (± 0.333)	0.12 (± 0.485)		
Suicidal ideation score - Change at 24 hrs	-0.40 (± 0.966)	-0.20 (± 0.523)		
Suicidal ideation score - Change at 48 hrs	0.00 (± 0.00)	-0.16 (± 0.375)		
Suicidal ideation score - Change at day 43	-0.11 (± 1.269)	0.12 (± 1.111)		
SSTS total score - Change at 24 hrs	-0.50 (± 1.269)	-0.20 (± 0.523)		
SSTS total score Change at 48 hrs	0.00 (± 0.00)	-0.16 (± 0.375)		

SSTS total score - Change at Day 43	-0.22 (± 1.563)	0.47 (± 2.503)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with treatment remissions (MADRS<7)

End point title	Percentage of Participants with treatment remissions (MADRS<7)

End point description:

Percentage of Participants with treatment remissions as assessed via (MADRS<7)

End point type	Secondary

End point timeframe:

24 hours, 48 hours, and 6 weeks (Day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Percentage of Participants				
number (not applicable)				
% of participants with remission at 24 hrs	9.1	20.0	0	11.1
% of participants with remission at 48 hrs	22.2	10.0	11.1	28.6
% of participants with remission at Day 43	25.0	37.5	0	16.7

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Percentage of Participants				
number (not applicable)				
% of participants with remission at 24 hrs	20.0	5.0		
% of participants with remission at 48 hrs	25.0	10.5		
% of participants with remission at Day 43	22.2	11.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Total Hamilton Anxiety Scale

End point title	Change from baseline in the Total Hamilton Anxiety Scale

End point description:

The Hamilton Anxiety Rating Scale (HAM-A) measures psychic anxiety and somatic anxiety symptoms based on a clinical assessment and patient interview. The scale has 14 items, with each item rated from 0-4, ranging from not present to very severe. A maximum score of 56 indicates the most severe case. (Hamilton 1959).

End point type	Secondary

End point timeframe:

Baseline, and at 6 weeks (day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
least squares mean (standard error)	-1.94 (± 2.0)	-5.69 (± 2.0)	-7.17 (± 2.0)	-3.83 (± 2.2)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
least squares mean (standard error)	-4.93 (± 2.0)	-4.80 (± 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary statistics of total Hamilton Anxiety scale - change from baseline

End point title	Summary statistics of total Hamilton Anxiety scale - change from baseline

End point description:

The Hamilton Anxiety Rating Scale (HAM-A) measures psychic anxiety and somatic anxiety symptoms based on a clinical assessment and patient interview. The scale has 14 items, with each item rated from 0-4, ranging from not present to very severe. A maximum score of 56 indicates the most severe case. (Hamilton 1959).

End point type	Secondary

End point timeframe:

Change from baseline at week 6 (Day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
arithmetic mean (standard deviation)	-2.6 (± 6.927)	-5.4 (± 4.565)	-6.8 (± 6.606)	-4.2 (± 9.432)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
arithmetic mean (standard deviation)	-5.4 (± 7.763)	-5.1 (± 5.651)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Total Koukopoulos Mixed Depression Rating Scale

End point title	Change from baseline in the Total Koukopoulos Mixed Depression Rating Scale

End point description:

The Koukopoulos Mixed Depression Rating Scale (KMDRS) assesses the excitatory or mixed nature in patients suffering from a Major Depressive Episode (MDE) as defined by DSM-5 criteria. This scale is meant to be used in conjunction with another scale that assess typical depression and anxiety symptoms. The scale contains 14 items to be evaluated by clinical assessment and patient interview on symptoms potentially experienced over the past week. Overall score increases with severity of symptoms and has a maximum score of 51. (Sani et al 2018).

End point type	Secondary

End point timeframe:

Baseline, 24 hours, 48 hrs, and 6 weeks (day 43)

End point values	MIJ821 0.16 mg/kg weekly	MIJ821 0.16 mg/kg biweekly	MIJ821 0.32 mg/kg weekly	MIJ821 0.32 mg/kg biweekly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	10	9
Units: Scores on a Scale				
least squares mean (standard error)				
Adjusted mean change from baseline to 24 hrs	-2.79 (± 0.9)	-2.38 (± 0.9)	-1.50 (± 1.0)	-2.46 (± 1.0)

Adjusted mean change from baseline to 48 hrs	-2.95 (± 1.0)	-1.03 (± 0.9)	-1.97 (± 1.0)	-3.43 (± 1.1)
Adjusted mean change from baseline to day 43	-1.18 (± 1.0)	-1.06 (± 1.0)	-1.55 (± 1.1)	-2.04 (± 1.2)

End point values	Ketamine 0.5 mg/kg weekly	Placebo weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	20		
Units: Scores on a Scale				
least squares mean (standard error)				
Adjusted mean change from baseline to 24 hrs	-1.28 (± 1.0)	-2.33 (± 0.7)		
Adjusted mean change from baseline to 48 hrs	0.01 (± 1.3)	-1.97 (± 0.7)		
Adjusted mean change from baseline to day 43	-1.68 (± 1.0)	-1.59 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Responders (>50% improvement in Bech-Rafaelsen Melancholia scale) and Melancholia and Mixed Depression Checklist factor.

End point title	Responders (>50% improvement in Bech-Rafaelsen Melancholia scale) and Melancholia and Mixed Depression Checklist factor.

End point description:

Percentage of Participants who responded. The first mixed depression checklist, created by Koukopoulos, has 8 criteria, which are marked as present or absent. If 3 or more criteria are marked present, then mixed depression would be diagnosed. The second mixed depression checklist, created by Angst, lists the 7 criteria for mania from DSM-5, which are marked as present or absent. If 3 or more criteria are marked present, excluding any duration criterion, then mixed depression would be diagnosed. The melancholia checklist, created by Ghaemi for this study, has 4 criteria, which are marked as present or absent. If 3 or more criteria are marked present, then melancholia would be diagnosed.

End point type	Secondary

End point timeframe:

24 hours, 48 hours, and 6 weeks (Day 43)

End point values	Koukopoulos	Angst	Ghaemi	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	9	9	
Units: Percentage of Participants				
number (not applicable)				
% who responded at 24 hrs - drugs	40.0	0	20.0	
% who responded at 24 hrs - placebo	0	0	100	
% who responded at 48 hrs - drugs	50.0	0	33.3	
% who responded at 48 hrs - placebo	0	0	50.0	

% who responded at Day 43 - drugs	55.6	0	44.4	
% who responded at Day 43- placebo	33.3	0	0	

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 plus 30 post treatment, up to a maximum duration of 66 days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	MIJ821 0.16 mg/kg weekly*
Reporting group description: MIJ821 0.16 mg/kg weekly*	
Reporting group title	MIJ821 0.16 mg/kg every other week
Reporting group description: MIJ821 0.16 mg/kg every other week	
Reporting group title	MIJ821 0.32 mg/kg weekly
Reporting group description: MIJ821 0.32 mg/kg weekly	
Reporting group title	MIJ821 0.32 mg/kg every other week
Reporting group description: MIJ821 0.32 mg/kg every other week	
Reporting group title	Ketamine
Reporting group description: Ketamine	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Total
Reporting group description: Total	

Serious adverse events	MIJ821 0.16 mg/kg weekly*	MIJ821 0.16 mg/kg every other week	MIJ821 0.32 mg/kg weekly
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Asthma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide threat			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MIJ821 0.32 mg/kg every other week	Ketamine	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	0 / 10 (0.00%)	1 / 20 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Major depression			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide threat			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 70 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			

subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide threat			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	MIJ821 0.16 mg/kg weekly*	MIJ821 0.16 mg/kg every other week	MIJ821 0.32 mg/kg weekly
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 11 (63.64%)	6 / 10 (60.00%)	7 / 10 (70.00%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	4
Feeling abnormal			
subjects affected / exposed	3 / 11 (27.27%)	1 / 10 (10.00%)	2 / 10 (20.00%)
occurrences (all)	4	1	8
Feeling of relaxation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Agitation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Anxiety			

subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Daydreaming			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Depersonalisation/derealisation disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Disinhibition			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dissociation			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Dissociative amnesia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Euphoric mood			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Illusion			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Irritability			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Sleep disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Sleep terror			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Time perception altered			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	6	3	0
Blood pressure systolic increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Poisoning deliberate			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Amnesia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	5 / 10 (50.00%)
occurrences (all)	5	0	11
Ataxia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Disturbance in attention			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	2 / 11 (18.18%)	3 / 10 (30.00%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Dysarthria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	4
Hypoaesthesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Paraesthesia			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	4 / 10 (40.00%)
occurrences (all)	2	1	9
Syncope			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Tunnel vision			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Hyperacusis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Asthenopia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Photophobia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Frequent bowel movements			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Urinary tract infection			

subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	MIJ821 0.32 mg/kg every other week	Ketamine	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 9 (66.67%)	6 / 10 (60.00%)	5 / 20 (25.00%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Feeling abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Feeling of relaxation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Confusional state			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1

Daydreaming			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Depersonalisation/derealisation disorder			
subjects affected / exposed	0 / 9 (0.00%)	5 / 10 (50.00%)	0 / 20 (0.00%)
occurrences (all)	0	22	0
Disinhibition			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	6	0
Dissociation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dissociative amnesia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Euphoric mood			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Illusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Sleep terror			

subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Time perception altered			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood pressure systolic increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Poisoning deliberate			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Amnesia			
subjects affected / exposed	3 / 9 (33.33%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	8	0	0
Ataxia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	6	0	0
Disturbance in attention			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 9 (11.11%)	2 / 10 (20.00%)	1 / 20 (5.00%)
occurrences (all)	1	5	2
Dysarthria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Hypoaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Memory impairment			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	1 / 20 (5.00%)
occurrences (all)	0	5	2
Sciatica			

subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Syncope			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tunnel vision			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Hyperacusis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 10 (20.00%)	0 / 20 (0.00%)
occurrences (all)	0	3	0
Eye disorders			
Asthenopia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	0 / 9 (0.00%)	3 / 10 (30.00%)	1 / 20 (5.00%)
occurrences (all)	0	4	1
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			

subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	2 / 10 (20.00%)	0 / 20 (0.00%)
occurrences (all)	0	6	0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 70 (52.86%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 70 (7.14%)		
occurrences (all)	7		
Feeling abnormal			
subjects affected / exposed	6 / 70 (8.57%)		
occurrences (all)	13		
Feeling of relaxation			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	2		
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Agitation			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	2 / 70 (2.86%)		
occurrences (all)	2		
Confusional state			
subjects affected / exposed	3 / 70 (4.29%)		
occurrences (all)	3		
Daydreaming			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	2		
Depersonalisation/derealisation			

disorder				
subjects affected / exposed	5 / 70 (7.14%)			
occurrences (all)	22			
Disinhibition				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	6			
Dissociation				
subjects affected / exposed	3 / 70 (4.29%)			
occurrences (all)	3			
Dissociative amnesia				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Euphoric mood				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Illusion				
subjects affected / exposed	2 / 70 (2.86%)			
occurrences (all)	2			
Insomnia				
subjects affected / exposed	3 / 70 (4.29%)			
occurrences (all)	3			
Irritability				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Mood swings				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Sleep disorder				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Sleep terror				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Time perception altered				
subjects affected / exposed	2 / 70 (2.86%)			
occurrences (all)	3			

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	3 / 70 (4.29%)		
occurrences (all)	9		
Blood pressure systolic increased			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Poisoning deliberate			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Amnesia			

subjects affected / exposed	10 / 70 (14.29%)			
occurrences (all)	24			
Ataxia				
subjects affected / exposed	3 / 70 (4.29%)			
occurrences (all)	9			
Disturbance in attention				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Dizziness				
subjects affected / exposed	10 / 70 (14.29%)			
occurrences (all)	14			
Dysarthria				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Dysgeusia				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Headache				
subjects affected / exposed	6 / 70 (8.57%)			
occurrences (all)	8			
Hypoaesthesia				
subjects affected / exposed	2 / 70 (2.86%)			
occurrences (all)	3			
Memory impairment				
subjects affected / exposed	3 / 70 (4.29%)			
occurrences (all)	4			
Paraesthesia				
subjects affected / exposed	3 / 70 (4.29%)			
occurrences (all)	8			
Sciatica				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences (all)	1			
Somnolence				
subjects affected / exposed	8 / 70 (11.43%)			
occurrences (all)	14			
Syncope				

subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Tunnel vision			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Hyperacusis			
subjects affected / exposed	2 / 70 (2.86%)		
occurrences (all)	3		
Eye disorders			
Asthenopia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	4 / 70 (5.71%)		
occurrences (all)	5		
Dyspepsia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Frequent bowel movements			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	4 / 70 (5.71%)		
occurrences (all)	8		
Vomiting			

subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2019	Amendment 01
02 July 2019	Amendment 02

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported