Clinical trial results:
An exploratory, blinded, randomized, placebo-controlled study in subjects with depressive disorder to investigate the effect of minocycline on relapse after successful intravenous ketamine/minocycline-induced (partial) symptoms response

Summary

EudraCT number	2012-002954-21
Trial protocol	BE NL ES
Global end of trial date	10 July 2014

Results information

Result version number	v1 (current)
This version publication date	23 June 2016
First version publication date	23 June 2016

Trial information

Trial identification

Sponsor protocol code	KETIVEDI2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01809340
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Archimedesweg 29, Leiden, Netherlands, 2333CM
Public contact	Clinical Registry Group, Janssen-Cilag International NV, 3171 524 21 66, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, 3171 524 21 66, ClinicalTrialsEU@its.jnj.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	10 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess whether the antidepressant response to intravenous (IV) ketamine can be maintained by minocycline compared to placebo.

Protection of trial subjects:

Safety and tolerability of the participants and assessment of suicidal ideation and behavior using the CSSRS, were evaluated by monitoring of adverse events (AEs), physical examination, body weight, supine vital signs, digital pulse oximetry, 12-lead electrocardiogram (ECG), and continuous ECG monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 June 2013
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	Belgium: 14
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Netherlands: 8
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	25
From 65 to 84 years	4

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 29 participants were enrolled with Major Depressive Disorder (MDD) or Bipolar Depression Disorder (BPD) of Type II were randomized and treated.

Period 1

Period 1 title	12-Day Treatment Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open Label: Ketamine/ Minocycline (12 Days)

Arm description:

Participants received intravenous infusion of 0.5 milligram/kilogram (mg/kg) of body weight ketamine over 40 minutes on Days 1, 3, 5, 8, 10, and 12 in combination with minocycline 100 mg, orally administered twice daily.

Arm type	Experimental
Investigational medicinal product name	Ketamine
Investigational medicinal product code	
Other name	Ketamine Hydrochloride
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered ketamine hydrochloride Intravenous (IV) injection at a dose of 50 milligram(s)/ 5 millilitre (mg/ml) over 40 minutes on Days 1, 3, 5, 8, 10, and 12.

Investigational medicinal product name	Minocycline Hydrochloride
Investigational medicinal product code	
Other name	Minocin - hard capsule - 100 mg
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with Minocycline 200 mg (milligrams) capsule (2*100mg=200mg) on day 1, and 100 mg twice daily on days 2 to 11 and 100 mg on the morning of day 12 orally.

Number of subjects in period 1	Open Label: Ketamine/ Minocycline (12 Days)
Started	29
Completed	29

Period 2

Period 2 title	6-Week Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ketamine non-responders: Minocycline

Arm description:

Participants without ketamine response (ketamine non-responders) in 12-day open label treatment phase self-administered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54.

Arm type	Experimental
Investigational medicinal product name	Minocycline Hydrochloride
Investigational medicinal product code	
Other name	Minocin - hard capsule - 100 mg
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with Minocycline 100 mg capsule twice daily from Day 12 to Day 54, orally.

Arm title	Ketamine responders: Minocycline

Arm description:

Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self administered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54.

Arm type	Experimental
Investigational medicinal product name	Minocycline Hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with Minocycline 100 mg capsule twice daily from Day 12 to Day 54, orally.

Arm title	Ketamine responders: Placebo

Arm description:

Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self administered placebo matching with minocycline orally twice daily from Day 12 to Day 54.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with placebo during treatment period.

Number of subjects in period 2[1]	Ketamine non-responders: Minocycline	Ketamine responders: Minocycline	Ketamine responders: Placebo
Started	5	7	7
Completed	4	7	5
Not completed	1	0	2
Other	1	-	-
Randomised but not treated	-	-	1
Lost to follow-up	-	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 10 participants who were ketamine non-responders from the 12-day Open Label Treatment Phase did not enter the optional 6-week Open label treatment phase.

Baseline characteristics

Reporting groups	
Reporting group title	Open Label: Ketamine/ Minocycline (12 Days)
Reporting group description:	
Participants received intravenous infusion of 0.5 milligram/kilogram (mg/kg) of body weight ketamine over 40 minutes on Days 1, 3, 5, 8, 10, and 12 in combination with minocycline 100 mg, orally administered twice daily.	

Reporting group values	Open Label: Ketamine/ Minocycline (12 Days)	Total	
Number of subjects	29	29	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	25	
From 65 to 84 years	4	4	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	50.5		
standard deviation	± 12.53	-	
Title for Gender Units: subjects			
Female	16	16	
Male	13	13	

End points

End points reporting groups

Reporting group title	Open Label: Ketamine/ Minocycline (12 Days)
Reporting group description:	
Participants received intravenous infusion of 0.5 milligram/kilogram (mg/kg) of body weight ketamine over 40 minutes on Days 1, 3, 5, 8, 10, and 12 in combination with minocycline 100 mg, orally administered twice daily.	
Reporting group title	Ketamine non-responders: Minocycline
Reporting group description:	
Participants without ketamine response (ketamine non-responders) in 12-day open label treatment phase self-administered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54.	
Reporting group title	Ketamine responders: Minocycline
Reporting group description:	
Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self administered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54.	
Reporting group title	Ketamine responders: Placebo
Reporting group description:	
Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self administered placebo matching with minocycline orally twice daily from Day 12 to Day 54.	

Primary: Percentage of subjects who were relapse-free (among responders) on Day54 (Week 6)

End point title	Percentage of subjects who were relapse-free (among responders) on Day54 (Week 6)[1]
End point description:	
A participants was defined as "relapsed" if Montgomery-Asberg Depression Rating Scale (MADRS) total score had returned to greater than or equal to 30 after at least the first dose administration of minocycline or placebo in the 6-week blinded, treatment phase. The Montgomery-Asberg Depression Rating Scale (MADRS) measures 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 score of 60. Higher scores represent a more severe condition by Treatment. Intent to treat (ITT) analysis set included all subjects who received at least 1 dose of study drug and had both baseline and at least 1 post-baseline MADRS total score. Data for this endpoint was collected from only who were ketamine responders.	
End point type	Primary
End point timeframe:	
Day 54 (Week 6)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not reported as inferential analysis was not performed as planned.

End point values	Ketamine responders: Minocycline	Ketamine responders: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: Percentage				
number (not applicable)	85.7	57.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MADRS total score from Day 12 to end-of-study (Day 54)

End point title	Change in MADRS total score from Day 12 to end-of-study (Day 54)

End point description:

The Montgomery-Asberg Depression Rating Scale (MADRS) measures 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 score of 60. Higher scores represent a more severe condition. ITT population. Here "n" signifies number of subjects who were analysed for this outcome measure at specific time points.

End point type	Secondary

End point timeframe:

Day 12 and Day 54

End point values	Ketamine responders: Minocycline	Ketamine responders: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 12 (n=7, 6)	9.6 (± 6.65)	8.2 (± 4.26)		
Change at Day 54 (n= 6, 2)	1 (± 2.53)	4.5 (± 2.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the MADRS total score from baseline during ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12)

End point title	Change in the MADRS total score from baseline during ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12)

End point description:

The Montgomery-Asberg Depression Rating Scale (MADRS) measures 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 score of 60. Higher scores represent a more severe condition. ITT population. Here "n" signifies number of subjects who were analysed for this outcome measure at specific time points.

End point type	Secondary

End point timeframe:

Day 1 Predose and Days 1, 3, 5, 8, 10 and 12

End point values	Open Label: Ketamine/ Minocycline (12 Days)			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Predose Day 1	33 (± 5)			
Change at Day 1 (n=29)	-8.7 (± 8.57)			
Change at Day 3 (n=29)	-11.9 (± 7.66)			
Change at Day 5 (n=29)	-14.2 (± 8.35)			
Change at Day 8 (n=29)	-15.7 (± 9.17)			
Change at Day 10 (n=28)	-17 (± 9.2)			
Change at Day 12 (n=26)	-15.6 (± 10.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the MADRS total score from baseline after the IV ketamine treatment phase (Days 20, 27, 34, 41, 48, and 54)

End point title	Change in the MADRS total score from baseline after the IV ketamine treatment phase (Days 20, 27, 34, 41, 48, and 54)

End point description:

The Montgomery-Asberg Depression Rating Scale (MADRS) measures 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 score of 60. Higher scores represent a more severe condition. ITT population. Here "n" signifies number of subjects who were analysed for this outcome measure at specific time points.

End point type	Secondary

End point timeframe:

Day 1 and days 20, 27, 34, 41, 48, and 54.

End point values	Ketamine responders: Minocycline	Ketamine responders: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: unit on a scale				
arithmetic mean (standard deviation)				
Day 1 Predose (n=7, 6)	33 (± 7.46)	33 (± 3.27)		
Change at Day 20 (n= 7, 6)	-19.9 (± 10.88)	-20 (± 7.97)		
Change at Day 27 (n= 6, 6)	-22 (± 8.37)	-17.3 (± 16.74)		
Change at Day 34 (n= 6, 5)	-20 (± 8.94)	-25.4 (± 5.59)		
Change at Day 41 (n= 6, 4)	-18.2 (± 9.6)	-17.3 (± 12.2)		
Change at Day 48 (n= 6, 3)	-20.3 (± 9.95)	-25 (± 6.08)		

Change at Day 54 (n= 6, 3)	-21.8 (± 8.42)	-23 (± 5.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Response during the IV ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12)

End point title	Percentage of Participants with Response during the IV ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12)

End point description:

End point type	Secondary

End point timeframe:

Days 1, 3, 5, 8, 10 and 12

End point values	Open Label: Ketamine/ Minocycline (12 Days)			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percentage of participants				
number (not applicable)	48			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Relapse

End point title	Median Time to Relapse

End point description:

End point type	Secondary

End point timeframe:

Day 12 up to End of Study (Day 54)

End point values	Ketamine responders: Minocycline	Ketamine responders: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Days				
median (full range (min-max))	(to)	(to)		

Notes:

[2] - Median levels were not reached due to the early stopping / small sample size.

[3] - Median levels were not reached due to the early stopping / small sample size.

Statistical analyses

No statistical analyses for this end point

Secondary: Columbia Suicide Severity Rating Scale (C-SSRS) Score

End point title	Columbia Suicide Severity Rating Scale (C-SSRS) Score

End point description:

End point type	Secondary

End point timeframe:

From Screening up to follow-up (Day 54)

End point values	Ketamine non-responders: Minocycline	Ketamine responders: Minocycline	Ketamine responders: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[4]	0[5]	0[6]	
Units: unit on a scale				
number (not applicable)				

Notes:

[4] - Data for this endpoint was not summarized and individual data were listed.

[5] - Data for this endpoint was not summarized and individual data were listed.

[6] - Data for this endpoint was not summarized and individual data were listed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Screening up to follow-up (Day 54)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Open Label: Ketamine/ Minocycline (12 Days)
Reporting group description:	
Participants received intravenous infusion of 0.5 milligram/kilogram of body weight (mg/kg) ketamine over 40 minutes on Days 1, 3, 5, 8, 10, and 12 in combination with minocycline 100 mg, orally administered twice daily.	
Reporting group title	Ketamine responders: Placebo
Reporting group description:	
Participants with ketamine response (ketamine responders) in 12-day open label treatment phase selfadministered placebo matching with minocycline orally twice daily from Day 12 to Day 54.	
Reporting group title	Ketamine responders: Minocycline
Reporting group description:	
Participants with ketamine response (ketamine responders) in 12-day open label treatment phase selfadministered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54.	
Reporting group title	Minocycline 100 mg BID Open Label 6 Weeks
Reporting group description:	
Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self administered placebo matching with minocycline orally twice daily from Day 12 to Day 54.	

Serious adverse events	Open Label: Ketamine/ Minocycline (12 Days)	Ketamine responders: Placebo	Ketamine responders: Minocycline
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Psychiatric disorders			
Anxiety			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 6 (16.67%)	0 / 7 (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

Serious adverse events	Minocycline 100 mg BID Open Label 6 Weeks		

Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Psychiatric disorders			
Anxiety			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
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	Open Label: Ketamine/ Minocycline (12 Days)	Ketamine responders: Placebo	Ketamine responders: Minocycline
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 29 (86.21%)	3 / 6 (50.00%)	6 / 7 (85.71%)
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 29 (3.45%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Hot flush			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 29 (10.34%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Feeling Abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	6	0	1
Feeling of Relaxation			
alternative assessment type:			

Systematic			
subjects affected / exposed	4 / 29 (13.79%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	8	0	0
Reproductive system and breast disorders			
Breast Tenderness			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Psychiatric disorders			
Affect Lability			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	4	0	2
Anxiety			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 29 (13.79%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	9	0	1
Bradyphrenia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Depressed Mood			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 29 (3.45%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	4	2	1
Dissociation			
alternative assessment type: Systematic			
subjects affected / exposed	12 / 29 (41.38%)	2 / 6 (33.33%)	2 / 7 (28.57%)
occurrences (all)	48	2	2
Elevated Mood			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Insomnia			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 29 (6.90%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Negative Thoughts			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Suicidal Ideation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 29 (3.45%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Dissociative disorder			
subjects affected / exposed	1 / 29 (3.45%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Investigations			
Blood Pressure Increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	5	0	1
Injury, poisoning and procedural complications			
Contusion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 29 (27.59%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	26	1	1
Dysarthria			
alternative assessment type: Systematic			

subjects affected / exposed	3 / 29 (10.34%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	11 / 29 (37.93%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	18	2	4
Hyperaesthesia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	1
Migraine			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 29 (13.79%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	9	0	0
Sciatica			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Eye disorders			
Diplopia			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 29 (13.79%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	7	0	1
Vision Blurred			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 29 (13.79%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	8	0	1
Gastrointestinal disorders			

Abdominal Discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Dry Mouth			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Hypoaesthesia Oral			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 29 (17.24%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	9	1	1
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 29 (6.90%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Muscle Tightness			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Infections and infestations			

Gastroenteritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash Pustular			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Tinea Pedis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Increased Appetite			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Minocycline 100 mg BID Open Label 6 Weeks		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)		
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Feeling Abnormal			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Feeling of Relaxation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast Tenderness			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Affect Lability			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Anxiety			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Bradyphrenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Depressed Mood			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dissociation			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Elevated Mood			
alternative assessment type:			

Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Insomnia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Negative Thoughts			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Suicidal Ideation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Tension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dissociative disorder			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Investigations			
Blood Pressure Increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dysarthria			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hyperaesthesia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Migraine			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Eye disorders			
Diplopia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Vision Blurred			

alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Gastrointestinal disorders Abdominal Discomfort alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Diarrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Dry Mouth alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Hypoaesthesia Oral alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Nausea alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Skin and subcutaneous tissue disorders Hyperhidrosis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Musculoskeletal and connective tissue disorders Muscle Tightness alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Myalgia			

alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Infections and infestations Gastroenteritis alternative assessment type: Systematic subjects affected / exposed occurrences (all) Rash Pustular alternative assessment type: Systematic subjects affected / exposed occurrences (all) Tinea Pedis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1		
Metabolism and nutrition disorders Increased Appetite alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2013	The first amendment was released to revise to facilitate participant recruitment (without changing the aims of the protocol) and provide further clarification regarding participant eligibility requirements.
18 March 2014	The second amendment was released to amend the criteria for Ketamine responder criteria were amended to reflect normal variation in response. Additionally the maximum number of concomitant psychotropic drugs were increased to better reflect clinical practice.

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.

Study was terminated prematurely due to slow recruitment resulting in expiration of trial supplies Inability to secure new trial supplies due to availability issues.

Notes: