Clinical trial results:
Intravenous ketamine for Treatment Resistant Depression: Exploring biomarkers of response and relapse
A double-blind, randomized controlled trial

Summary

EudraCT number	2016-001715-21
Trial protocol	BE
Global end of trial date	29 January 2019

Results information

Result version number	v1 (current)
This version publication date	12 February 2020
First version publication date	12 February 2020

Trial information

Trial identification

Sponsor protocol code	S59102

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	UZ Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Carmen Schiweck, UZ Leuven, +32 016346798, stephan.claes@uzleuven.be
Scientific contact	Carmen Schiweck, UZ Leuven, +32 0465273027, carmen.schiweck@kuleuven.be

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	Interim
Date of interim/final analysis	29 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2019
Global end of trial reached?	Yes
Global end of trial date	29 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To replicate efficacy of intravenous ketamine in Treatment resistant depressed patients in a Belgian sample

Protection of trial subjects:

availability of emergency medication at study site, minitoring of vital signs, constant supervision during drug administration and 4h post administration; follow-up of adverse events and report to the eudravigilance database

Background therapy:

general antidepressant medication as described by current psychiatrist or physician; other medication not prohibited by the study protocol

Evidence for comparator:

The placebo is approximately 0.9 percent solution of sodium chloride and is used to compare to the study drug, it has proven successful in previous clinical trials with ketamine

Actual start date of recruitment	21 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	52

From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment has been ongoing since end december 2016. Recruitment was slow and we did not achieve the initial number of participants. The final inclusion was 29 patients and 26 controls.

Pre-assignment

Screening details:

Before screening patients need to have stable medication for 4 weeks. Patients excluded for participation in the study show symptoms of psychosis, alcohol abuse, other physical disease or are not interested to participate. The requirement for stable medication for at least 4 weeks limits inclusion by treating physicians.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

At baseline patients have a one week period of data collection. All patients are following their usual treatment and no study drug is administered. No person involved knows the group membership up to this point.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ketamine

Arm description:

patients who will receive ketamine during randomization

Arm type	Experimental
Investigational medicinal product name	ketalar
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Infusion of 0.5mg/kg of bodyweight over 40 minutes

Arm title	Placebo

Arm description:

patients who will recieve placebo during randomization

Arm type	Placebo
Investigational medicinal product name	0,9% sodium chloride solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intracavernous use

Dosage and administration details:

0,9% sodium chloride solution administered over 40 min intraveneously

Number of subjects in period 1[1]	Ketamine	Placebo
Started	21	7
Completed	21	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 26 healthy controls completed the baseline but did not continue to randomization, as foreseenin the protocol

Period 2

Period 2 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

All involved study personnel is blinded to the study drug membership (placebo/ketamine). Only the pharmacist knows the content of the provided study medication and is not to reveal its content to the study personnel.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

1/3 of the patients receive placebo

Arm type	Placebo
Investigational medicinal product name	0,9% sodium chloride solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intracavernous use

Dosage and administration details:

0,9% sodium chloride solution administered over 40 min intraveneously

Arm title	Ketamine

Arm description:

2/3 of participants receive ketamine

Arm type	Experimental
Investigational medicinal product name	ketalar
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Infusion of 0.5mg/kg of bodyweight over 40 minutes

Number of subjects in period 2	Placebo	Ketamine
Started	7	21
Completed	7	21

Period 3	
Period 3 title	Follow Up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor
Blinding implementation details: idem to before	
Arms	
Are arms mutually exclusive?	Yes
Arm title	Ketamine
Arm description: This period is the follow up of the randomization phase, no medication was administered	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Placebo
Arm description: Follow-Up of Placebo arm	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Ketamine	Placebo
Started	21	7
Completed	20	7
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ketamine
Reporting group description: patients who will receive ketamine during randomization	
Reporting group title	Placebo
Reporting group description: patients who will recieve placebo during randomization	

Reporting group values	Ketamine	Placebo	Total
Number of subjects	21	7	28
Age categorical			
Subjects are all above 18 and younger than 85 at this stage of inclusion			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	7	26
From 65-84 years	2	0	2
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	44.95	45.43	
standard deviation	± 14.72	± 10.77	-
Gender categorical			
Both male an female particpants are being collected			
Units: Subjects			
Female	13	4	17
Male	8	3	11
SMOKER			
Current Smoking Status of Subjects			
Units: Subjects			
SMOKER	4	1	5
NONSMOKER	17	6	23
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean			
standard deviation	±	±	-
Depression severity			
Depression Severity as measured by the Hamilton Depression Rating Scale			
Units: points			
arithmetic mean			

standard deviation	±	±	-

Subject analysis sets

Subject analysis set title	Depressed
Subject analysis set type	Sub-group analysis
Subject analysis set description: patients who are depressed and received ketamine	
Subject analysis set title	Healthy control
Subject analysis set type	Sub-group analysis
Subject analysis set description: Healthy controls not receiving ketamine	

Reporting group values	Depressed	Healthy control	
Number of subjects	28	26	
Age categorical			
Subjects are all above 18 and younger than 85 at this stage of inclusion			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	26	26	
From 65-84 years	2	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	45.07	42.69	
standard deviation	± 13.65	± 11.80	
Gender categorical			
Both male an female particpants are being collected			
Units: Subjects			
Female	17	13	
Male	11	13	
SMOKER			
Current Smoking Status of Subjects			
Units: Subjects			
SMOKER	5	3	
NONSMOKER	23	23	
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean	28.47	24.54	
standard deviation	± 5.06	± 3.94	
Depression severity			
Depression Severity as measured by the Hamilton Depression Rating Scale			

Units: points			
arithmetic mean	21.07	2.0	
standard deviation	± 3.68	± 1.83	

End points

End points reporting groups

Reporting group title	Ketamine
Reporting group description: patients who will receive ketamine during randomization	
Reporting group title	Placebo
Reporting group description: patients who will recieve placebo during randomization	
Reporting group title	Placebo
Reporting group description: 1/3 of the patients receive placebo	
Reporting group title	Ketamine
Reporting group description: 2/3 of participants receive ketamine	
Reporting group title	Ketamine
Reporting group description: This period is the follow up of the randomization phase, no medication was administered	
Reporting group title	Placebo
Reporting group description: Follow-Up of Placebo arm	
Subject analysis set title	Depressed
Subject analysis set type	Sub-group analysis
Subject analysis set description: patients who are depressed and received ketamine	
Subject analysis set title	Healthy control
Subject analysis set type	Sub-group analysis
Subject analysis set description: Healthy controls not receiving ketamine	

Primary: Depression score change Day 8

End point title	Depression score change Day 8

End point description:

Depression scores on the Hamilton depression scale and the quick inventory of depressive symptomatology. Severity scores for the HAMD can be found below:
0-7 = Normal
8-13 = Mild Depression
14-18 = Moderate Depression
19-22 = Severe Depression
≥ 23 = Very Severe Depression.

Depressions cores are used as continuous variables.

End point type	Primary

End point timeframe:

Depression score per group on Day 8 (4H post Ketamine)

End point values	Placebo	Ketamine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	21		
Units: points				
arithmetic mean (standard deviation)	19.57 (± 4.86)	18.86 (± 4.67)		

Statistical analyses

Statistical analysis title	Day 8 depression difference groups
Statistical analysis description:	
t test between placebo and ketamine groups to estimate a significant difference between both. Similar analysis are performed for day 9, day 15 and follow-up.	
Comparison groups	Placebo v Ketamine
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7409
Method	t-test, 2-sided
Parameter estimate	t value
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.396
upper limit	3.968

Primary: Depression score Day 9

End point title	Depression score Day 9
End point description:	
This is the score 24 h post ketamine	
End point type	Primary
End point timeframe:	
Day 9 (24h post ketamine)	

End point values	Placebo	Ketamine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	21		
Units: points				
arithmetic mean (standard deviation)	13.29 (± 5.35)	15.81 (± 5.37)		

Statistical analyses

Statistical analysis title	Day 9 Depression Severity change
Comparison groups	Placebo v Ketamine
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.304
Method	t-test, 2-sided
Parameter estimate	t value
Point estimate	1.0805
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6557
upper limit	7.7034

Primary: Depression Score change Day 15	
End point title	Depression Score change Day 15
End point description:	
End point type	Primary
End point timeframe:	
Depression Score on Day 15 (7 days post ketamine)	

End point values	Placebo	Ketamine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	20		
Units: points				
arithmetic mean (standard deviation)	14.71 (± 6.73)	19.3 (± 6.33)		

Statistical analyses

Statistical analysis title	D15 depression severity between groups
Comparison groups	Placebo v Ketamine
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1462
Method	t-test, 2-sided
Parameter estimate	t value
Point estimate	1.576

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.898
upper limit	11.07

Primary: Depression change score Day 21

End point title	Depression change score Day 21
End point description:	
End point type	Primary
End point timeframe:	
Depression change score follow up (2 weeks post ketamine)	

End point values	Placebo	Ketamine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	21		
Units: points				
arithmetic mean (standard deviation)	16 (± 6.32)	18.81 (± 6.06)		

Statistical analyses

Statistical analysis title	FU comparison depression severity
Statistical analysis description:	
depression severity between groups at FU	
Comparison groups	Placebo v Ketamine
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3281
Method	t-test, 2-sided
Parameter estimate	T value
Point estimate	1.0283
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.282
upper limit	8.901

Primary: Baseline Depression Scores Placebo Ketamine

End point title	Baseline Depression Scores Placebo Ketamine

End point description: Baseline Depression Score	
End point type	Primary
End point timeframe: Baseline depression scores	

End point values	Placebo	Ketamine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	21		
Units: points				
arithmetic mean (standard deviation)	21.86 (± 4.56)	20.81 (± 3.43)		

Statistical analyses

Statistical analysis title	Baseline difference Placebo Ketamine
Statistical analysis description: T test of depression severity difference between placebo and Ketamine	
Comparison groups	Placebo v Ketamine
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	t value
Point estimate	-0.55736
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.35
upper limit	3.25

Primary: Resp vs non Resp ket and placebo	
End point title	Resp vs non Resp ket and placebo
End point description: comparison of proportions between responders and non responders	
End point type	Primary
End point timeframe: Responders and partial responders on day 9 compared to Baseline	

End point values	Placebo	Ketamine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	21		
Units: Subjects				
non responder	2	13		
responder	3	3		
partial responder	2	5		

Statistical analyses

Statistical analysis title	chi square responder

Statistical analysis description:

chi square test between responder/non responder proportions per group

Comparison groups	Ketamine v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.208 [1]
Method	Chi-squared

Notes:

[1] - The X2 is 3.1365, df=2, p value =0.2084

Primary: Depressive sympotm change over time per group

End point title	Depressive sympotm change over time per group

End point description:

Here we assess a simple linear mixed model to assess the change of depressive symptoms over time. We include an interaction effect of Treatment and timepoint to see if the groups differ at any given timepoint and a random intercept.

The model is as follows:
Depression severity ~ timepoint*treatment condition+ random intercept

End point type	Primary

End point timeframe:

spans the entire study period from baseline to follow up

End point values	Placebo	Ketamine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	21		
Units: points				
number (not applicable)	7	21		

Attachments (see zip file)	Resultas Linear Mixed Model/lmer Ketamine.xlsx

Statistical analyses

Statistical analysis title	Linear Mixed Model Treatment over time

Statistical analysis description:

Treatment over time is assessed with a linear model including timepoint, treatment condition and their interaction.

Comparison groups	Placebo v Ketamine
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.6431 [3]
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	1.0476
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.43
upper limit	5.53
Variability estimate	Standard error of the mean
Dispersion value	2.25

Notes:

[2] - Linear mixed model to determine development over time.

[3] - We here tested whether any timepoint or group effect is significant at the $p<0.05$ level.
The platform does not allow to fill in several p values which is required for this analysis. Therefore we here report the overall group effect of the model.

Other pre-specified: Baseline Healthy vs Depressed Depression Severity

End point title	Baseline Healthy vs Depressed Depression Severity

End point description:

Comparison of Hamilton Depression Rating scale between healthy controls and entire depressed group

End point type	Other pre-specified

End point timeframe:

Baseline comparison

End point values	Depressed	Healthy control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	26		
Units: points				
arithmetic mean (standard deviation)	21.07 (± 3.68)	2 (± 1.83)		

Statistical analyses

Statistical analysis title	Difference HC and depressed

Statistical analysis description:

Anova test comparing healthy controls and depressed patients at baseline regarding depression severity

Comparison groups	Depressed v Healthy control

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-19.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.65
upper limit	-17.49

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events are assessed during the whole study period.	
Adverse event reporting additional description: An independent company (The Clinical Company) reports serious adverse events to the FAGG	
Assessment type	Systematic

Dictionary used	
Dictionary name	SAFTEE questionnaire
Dictionary version	1

Reporting groups	
Reporting group title	depressed patients
Reporting group description: patients with depression	
Reporting group title	healthy controls
Reporting group description: -	

Serious adverse events	depressed patients	healthy controls	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Acute suicidal ideation with psychological decompensation	Additional description: the patient experinced decompensation after feeling no improvement in depressive sympotms after the ketamine/placebo infusion. The clinicians decided to hsopitalize the patient.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	depressed patients	healthy controls	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 28 (89.29%)	0 / 26 (0.00%)	
Vascular disorders			
migraine	Additional description: not related to IMP		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Nausea systematic	Additional description: occured post infusion IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Fatigue/tired systematic	Additional description: reported post infusion IMP		
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Dizziness	Additional description: 10 of them reported during infusion IMP , one post		
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 28 (39.29%)	0 / 26 (0.00%)	
occurrences (all)	11	0	
Headache systematic	Additional description: occured post infusion IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
Dry mouth systematic	Additional description: both occured post infusion IMP		
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Stiffness	Additional description: post infusion but not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Confusional state	Additional description: occured during infusion , related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Diplopia	Additional description: during infusion , related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Tremor systematic	Additional description: post infusion IMP but not related		
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Oral pain	Additional description: post infusion but not related to IMP		

subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hot flush systematic	Additional description: hot and cold flushes, pre infusion IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
paresthesia hands	Additional description: occured during infusion, related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
sore throat systematic	Additional description: post infusion but not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Pruritus	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Menstruation irregular	Additional description: bleedings between menstruation, menstruation accompanied by cramps post infusion IMP but not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Somnolence	Additional description: during infusion, related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
muscle pain	Additional description: occured post infusion, but not related to IMP		
subjects affected / exposed	3 / 28 (10.71%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
fatigue/tired non-systematic	Additional description: occured post infusion IMP, related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
headache non-systematic			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
dry mouth non-systematic	Additional description: 2 of them reported during infusion IMP, 1 post infusion. All of them related to IMP		
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 28 (10.71%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
tremor non-systematic	Additional description: occured during infusion, related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
hot flush non-systematic	Additional description: during ketamin infusion reported by patient		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
sore throat non-systematic	Additional description: not related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
worsening dizziness	Additional description: occured during infusion IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
worsening headache	Additional description: patient experienced this event pre infusion IMP (not related)		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
worsening blurry vision	Additional description: 1 patient experienced this event pre infusion IMP (not related) and 1 during infusion IMP (related)		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
sensitive breast	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
pain breast	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
change of taste	Additional description: not related to IMP		

subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
increased thirst	Additional description: post infusion but not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
decreased sense of smell	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
decreased interest in sex	Additional description: not related to IMP		
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
pain joints	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
unstable stand on feet	Additional description: psot infusion IMP but not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
trembling	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
rigidity	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
bruising	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
excited	Additional description: occured post infusion but not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
anxiety	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
irritable	Additional description: not related to IMP		
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
shivering	Additional description: during infusion IMP		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
worsening dry mouth systematic	Additional description: during infusion		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
worsening dry mouth non-systematic	Additional description: related to IMP, during infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
light-headed	Additional description: during infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
reduced awareness	Additional description: related to IMP, during infusion		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
difficulties with speaking systematic	Additional description: post infusion IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
difficulties with speaking non-systematic	Additional description: during infusion, related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
insensibility/tingles	Additional description: not related to IMP, pre infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
cardial problems	Additional description: during infusion IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
stiff muscles	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

allergic reaction	Additional description: post infusion IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
nightmares	Additional description: post infusion IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
memory problem	Additional description: post infusion IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
excessive sweating	Additional description: related to IMP, post infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
sedated feeling	Additional description: related to IMP, during infusion .One patient overall sedated feeling, another sedated feeling moth and another one sedated feeling fingers		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 28 (10.71%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
paresthesia	Additional description: related to IMP, during infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
increased saliva production	Additional description: related to IMP, during infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
strange taste in mouth	Additional description: related to IMP, during infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
balance disorder	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

nervosity	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
restlegg legs	Additional description: related to IMP, during infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
hyperventilation	Additional description: during infusion IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Apnoea	Additional description: post infusion but not related to IMP		
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Auto-mutilation	Additional description: occured Post infusion but not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Concentration impairment	Additional description: occured post infusion, but not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Acute suicidal ideation & Psychological decompensation	Additional description: Also added as serious advent because hospitalization was required. The mental health state of this patient did not change majorly in comparison to before the administration of study drug, but as no improvement was seen the patient was hospitalized.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Stress	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Restlessness	Additional description: not related to IMP		
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Blood pressure fluctuation	Additional description: occured during infusion, related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

oedema feet	Additional description: post infusion but not related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain	Additional description: post infusion, not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred systematic	Additional description: one pre infusion, one post infusion		
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
light sensitivity	Additional description: post administration IMP, related		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
vision blurred non-systematic	Additional description: 3 of them occured during infusion, one post infusion IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 28 (14.29%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
swollen eyes	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting	Additional description: Patient started vomiting during ketamine/placebo infusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
stomach pain	Additional description: after ketamin infusion		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
nausea non-systematic	Additional description: all of them occured during infusion IMP, related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 28 (14.29%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
problems stomach	Additional description: post infusion but not related to IMP		

subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
abdominal cramps	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
gastro-intestinal complaints	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
excanthema	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
increased frequency urination	Additional description: not related to IMP		
subjects affected / exposed	2 / 28 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
elavated TSH in blood	Additional description: pre Infusion IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Gingivitis	Additional description: post infusion but not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
chlamydia trachomatis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
oral ulcer	Additional description: post infusion IMP, but no related		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
flu	Additional description: not related to IMP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

loss of appetite	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
increased appetite	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Decreased appetite	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
weight gain	Additional description: not related to IMP		
subjects affected / exposed	1 / 28 (3.57%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2017	Minor improvements were made to the protocol; no major changes
01 August 2017	Correction of small mistakes in protocol that were made previously
13 November 2017	Add French speaking, Belgian participants and allow for inclusion of BPD I patients

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.

Covariates and transformations of data still need to be applied; similarly, immune data is not yet available and will be included at a later moment.

Notes: