



## Clinical trial results:

### Brain Network Dysfunction as a Model for Schizophrenia: Connectivity Alterations using Ketamine and pharmacological Magnetic Resonance Imaging

#### Summary

EudraCT number	2010-022772-31
Trial protocol	AT
Global end of trial date	27 August 2012

#### Results information

Result version number	v1 (current)
This version publication date	20 October 2019
First version publication date	20 October 2019

#### Trial information

##### Trial identification

Sponsor protocol code	20100812v2
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01394757
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Waehringer Guertel 18-20, Vienna, Austria, 1090
Public contact	Assoc.-Prof. Rupert Lanzenberger, MD, Medical University of Vienna, +431 4040035760, rupert.lanzenberger@meduniwien.ac.at
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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	09 April 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 August 2012
Global end of trial reached?	Yes
Global end of trial date	27 August 2012
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate time-dependent changes in functional connectivity associated with ketamine.

Protection of trial subjects:

-Patients were observed by a medical doctor during the entire experimental procedures.

-During MRI measurements vital parameters (ECG, heart rate, respiratory rate) were monitored at all times.

-In case of termination of the MRI measurement by the participants, debriefing was done with the MD in charge with the possibility of drug application in case of side effects caused by the study drug.

-After the MRI measurements participants were observed in the clinical setting for a minimum of 2 hours in order to ensure the lack of side effects.

Background therapy:

-

Evidence for comparator: -

Actual start date of recruitment	06 June 2011
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	Austria: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	41
From 65 to 84 years	0



## Subject disposition

### Recruitment

Recruitment details:

Recruitment was performed via advertisement on dedicated message boards in the General Hospital of Vienna

### Pre-assignment

Screening details:

Approximately 100 potential participants were screened via telephone, 54 were thoroughly examined with regards to physical and psychiatric health. After this screening visit 51 participants were included in the study.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Placebo at MRI1/ Ketamine at MRI2
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Arm description:

Using a cross-over design participants were randomized to get either ketamine or placebo during the first MRI-measurement.

Arm type	Experimental
Investigational medicinal product name	esketamine hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study drug diluted in 0.9% NaCl. First administration of a bolus of 0.11 mg/kg body weight for 1 minute, followed by a maintenance infusion of 0.12 mg/kg body weight for 19 minutes.

<b>Arm title</b>	Ketamine at MRI 1/ Placebo at MRI 2
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Arm description:

Using a cross-over design participants were randomized to get either ketamine or placebo during the first MRI-measurement.

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

Dosage and administration details:

55 ml of 0.9 % NaCl was used as placebo.

<b>Number of subjects in period 1</b>	Placebo at MRI1/ Ketamine at MRI2	Ketamine at MRI 1/ Placebo at MRI 2
Started	21	20
MRI measurement completed	18	17
Completed	18	17
Not completed	3	3
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	2
Protocol deviation	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo at MRI1/ Ketamine at MRI2
Reporting group description: Using a cross-over design participants were randomized to get either ketamine or placebo during the first MRI-measurement.	
Reporting group title	Ketamine at MRI 1/ Placebo at MRI 2
Reporting group description: Using a cross-over design participants were randomized to get either ketamine or placebo during the first MRI-measurement.	

Reporting group values	Placebo at MRI1/ Ketamine at MRI2	Ketamine at MRI 1/ Placebo at MRI 2	Total
Number of subjects	21	20	41
Age categorical 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)	21	20	41
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	24.7	24.7	
standard deviation	± 5.2	± 4.1	-
Gender categorical Units: Subjects			
Female	10	8	18
Male	11	12	23

### Subject analysis sets

Subject analysis set title	Main Trial-resting-state measurement
Subject analysis set type	Sub-group analysis
Subject analysis set description: Only subjects who completed both MRI measurements in the main trial and there was sufficient data quality for the analysis were included in the analysis.	

Reporting group values	Main Trial-resting- state measurement		
Number of subjects	35		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	35		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	25.2		
standard deviation	± 4.8		
Gender categorical			
Units: Subjects			
Female	16		
Male	19		

## End points

### End points reporting groups

Reporting group title	Placebo at MRI1/ Ketamine at MRI2
Reporting group description: Using a cross-over design participants were randomized to get either ketamine or placebo during the first MRI-measurement.	
Reporting group title	Ketamine at MRI 1/ Placebo at MRI 2
Reporting group description: Using a cross-over design participants were randomized to get either ketamine or placebo during the first MRI-measurement.	
Subject analysis set title	Main Trial-resting-state measurement
Subject analysis set type	Sub-group analysis
Subject analysis set description: Only subjects who completed both MRI measurements in the main trial and there was sufficient data quality for the analysis were included in the analysis.	

### Primary: Functional connectivity

End point title	Functional connectivity
End point description:	
End point type	Primary
End point timeframe: Ketamine condition vs. Placebo condition, baseline vs. drug condition	

End point values	Placebo at MRI1/ Ketamine at MRI2	Ketamine at MRI 1/ Placebo at MRI 2	Main Trial-resting-state measurement	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	18	17	35	
Units: BOLD signal				
number (not applicable)	18	17	35	

### Statistical analyses

Statistical analysis title	repeated-measures ANOVA
Statistical analysis description: Interaction effect of time (time blocks of infusion vs. baseline) and drug (ketamine vs. Placebo)	
Comparison groups	Placebo at MRI1/ Ketamine at MRI2 v Ketamine at MRI 1/ Placebo at MRI 2

Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	other
P-value	$\leq 0.05$
Method	ANOVA

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:  
during entire trial

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	All subjects
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Reporting group description: -

<b>Serious adverse events</b>	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

<b>Non-serious adverse events</b>	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 41 (12.20%)		
Psychiatric disorders			
claustrophobia, Panic reaction			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2011	In order to ensure the best possible implementation of the main trial, to optimize the standardized study drug application, to assess start and time-course of ketamine effects and to define the optimal ketamine dosage a pilot trial was performed. In this open trial 11 participants were included, 10 participants completed the pilot-study

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25896256>