



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 |
|-----------------------|------------|

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 |
| Scientific contact | Assoc.-Prof. Rupert Lanzenberger, MD, Medical University of Vienna, +431 4040035760, rupert.lanzenberger@meduniwien.ac.at |

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 |

| | |
|-------------------|---|
| 85 years and over | 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 |
| Arm title | Placebo at MRI1/ Ketamine at MRI2 |

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.

| | |
|------------------|-------------------------------------|
| Arm title | Ketamine at MRI 1/ Placebo at MRI 2 |
|------------------|-------------------------------------|

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.

| Number of subjects in period 1 | 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 | ≤ 0.05 |
| Method | ANOVA |

Adverse events

Adverse events information

Timeframe for reporting adverse events:
during entire trial

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | All subjects |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events | 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 %

| Non-serious adverse events | 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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