



## Clinical trial results:

### Ketamine for relapse prevention in recurrent depressive disorder: a randomised, controlled pilot trial

#### Summary

EudraCT number	2015-002020-37
Trial protocol	IE
Global end of trial date	28 May 2018

#### Results information

Result version number	v1 (current)
This version publication date	16 January 2020
First version publication date	16 January 2020
Summary attachment (see zip file)	KINDRED Trial Report (KIND Trial Report final.docx)

#### Trial information

##### Trial identification

Sponsor protocol code	20/15
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02661061
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	St Patrick's Mental Health Services
Sponsor organisation address	Steevens' Lane, Dublin, Ireland, Dublin 8
Public contact	Martha Finnegan, St Patrick's University Hospital , 00353 12493385, mfinneg@tcd.ie
Scientific contact	Martha Finnegan, St Patrick's University Hospital , 00353 12493385, mfinneg@tcd.ie

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	06 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2018
Global end of trial reached?	Yes
Global end of trial date	28 May 2018
Was the trial ended prematurely?	Yes

Notes:

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**General information about the trial**

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Main objective of the trial:

The aim of this trial is to assess ketamine for reducing relapse in successfully treated recurrent depressive disorder (RDD).  
We hypothesise that ketamine will reduce six month relapse rates following successful treatment of depression.

Protection of trial subjects:

Independent ethics approval was sought and informed consent procedures were followed as per the trial protocol. Interventions were designed to minimise the potential for distress and participants were accompanied by researchers at all times during interventions.

Background therapy:

Participants continued on usual therapy throughout the trial. A detailed description of prescribed medication classes and frequencies is contained in the report.

Evidence for comparator:

Ketamine is a competitive glutamate N-methyl-D-aspartate receptor (NMDAR) antagonist with a half-life of 2-3 hours. Ketamine has a remarkably rapid antidepressant effect, targeting core symptoms in treatment-resistant depression when given as single sub-anaesthetic doses (usually a 40 minute 0.5 mg/kg intravenous infusion). It was chosen as the investigative medicinal product as it has not yet been investigated as a potential agent in depression relapse prevention. An active comparator, midazolam, was chosen as previously used by others in controlling for ketamine's potential psychotomimetic effects. Midazolam is a psychoactive medication which may theoretically improve blinding by controlling for some of the effects of the investigative medicinal product, ketamine.

Actual start date of recruitment	07 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Ireland: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

Notes:

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**Subjects enrolled per age group**

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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)	8
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited at admission to St Patrick's University Hospital for treatment of DSM-IV-diagnosed recurrent unipolar depression and followed-up weekly to assess recovery according to standard criteria. Treatment-as-usual continued throughout the entire trial. Responders were invited to be randomised.

### Pre-assignment

Screening details:

Clinical notes of newly admitted patients were screened for exclusion criteria and then patients who did not have clear exclusion factors were approached by a researcher to request verbal consent for advanced screening such as a HRSD-24 or sMMSE assessment. Patients who met all eligibility criteria were then provided with information.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Blinding implementation details:

Randomisation by sealed-envelope system using a computerised random allocation was performed independently by statisticians at the Centre for Training and Analysis in Research at University College Dublin (CTSAR). Raters and participants were blinded to allocation. Success of blinding of participants and raters was assessed after the first infusion. Both groups continued usual care during the randomised treatment phase and thereafter.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Ketamine

Arm description:

Participants were randomly allocated in a 1:1 ratio to an eight-week course of either two-weekly ketamine at 0.5mg/kg or the active comparator midazolam at 0.045mg/kg, in 50 ml of saline over 40 minutes, as per previous ketamine trials.

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

Dosage and administration details:

Investigative Medicinal Product - Ketamine Hydrochloride 10 mg/ml infusion at 0.5mg/kg (Pfizer Healthcare Ireland) made up as 50ml colourless saline solution and administered intravenously over 40 minutes via syringe driver pump.

<b>Arm title</b>	Midazolam
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Arm description:

Active Comparator - Midazolam Hydrochloride (Hypnovel) 10mg/5ml solution at 0.045mg/kg (Roche Products Ireland Ltd) made up as 50ml colourless saline solution and administered intravenously over 40 minutes via syringe driver pump.

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

Dosage and administration details:

Active Comparator - Midazolam Hydrochloride (Hypnovel) 10mg/5ml solution at 0.045mg/kg (Roche Products Ireland Ltd) made up as 50ml colourless saline solution and administered intravenously over 40 minutes via syringe driver pump.

<b>Number of subjects in period 1</b>	Ketamine	Midazolam
Started	5	4
Completed	3	2
Not completed	2	2
Relapse during treatment	1	1
Travel	1	1

## Baseline characteristics

## End points

### End points reporting groups

Reporting group title	Ketamine
Reporting group description: Participants were randomly allocated in a 1:1 ratio to an eight-week course of either two-weekly ketamine at 0.5mg/kg or the active comparator midazolam at 0.045mg/ kg, in 50 ml of saline over 40 minutes, as per previous ketamine trials.	
Reporting group title	Midazolam
Reporting group description: Active Comparator - Midazolam Hydrochloride (Hypnovel) 10mg/5ml solution at 0.045mg/kg (Roche Products Ireland Ltd) made up as 50ml colourless saline solution and administered intravenously over 40 minutes via syringe driver pump.	

### Primary: Randomisation rate

End point title	Randomisation rate <sup>[1]</sup>
End point description: The main purpose of this pilot study was to assess trial processes to help inform a future definitive trial. Therefore, the primary endpoint is a feasibility outcome, randomisation rate. Participants were recruited at admission to St Patrick's University Hospital for treatment of DSM-IV-diagnosed recurrent unipolar depression and followed-up weekly to assess recovery according to standard criteria. Recruitment commenced Dec 2015 and was paused in Nov 2016 due to staff unavailability due to grant contract difficulties, resolved in April 2017. Researchers commenced employment May 2017 and recruitment recommenced May 16th, 2017. In total n=3437 admissions were screened for eligibility and only n=103 of these were eligible, including after a trial protocol amendment to widen eligibility. 27% of eligible participants or n=28 participants were recruited to the monitoring phase, of which n=12 were eligible for the randomised treatment phase. In total only nine participants were randomised.	
End point type	Primary
End point timeframe: Entire trial	

#### 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: This pilot trial was designed to assess trial processes. Therefore, the primary endpoint is a feasibility outcome - randomisation rate. This does not lend itself to statistical analysis and trial participant numbers are in this case too low to compare any outcome across treatment groups.

End point values	Ketamine	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: Participants	5	4		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire trial

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Ketamine
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Reporting group description:

Participants were randomly allocated in a 1:1 ratio to an eight-week course of either two-weekly ketamine at 0.5mg/kg or the active comparator midazolam at 0.045mg/ kg, in 50 ml of saline over 40 minutes, as per previous ketamine trials.

Reporting group title	Midazolam
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Reporting group description:

Active Comparator - Midazolam Hydrochloride (Hypnovel) 10mg/5ml solution at 0.045mg/kg (Roche Products Ireland Ltd) made up as 50ml colourless saline solution and administered intravenously over 40 minutes via syringe driver pump.

Serious adverse events	Ketamine	Midazolam	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Ketamine	Midazolam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	
Immune system disorders			
Delayed hypersensitivity reaction	Additional description: Possible delayed hypersensitivity reaction, consisting of rash and hypertension with no airway interference or swelling, resolved within hours and did not require treatment.		
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Urticaria	Additional description: Pruritis and urticaria two days after treatment clinic causing discomfort. There were no associated abnormalities in vital signs or laboratory testing. The symptoms resolved quickly and completely on instituting of oral antihistamine.		



subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2016	<p>An approved amendment to the Trial Protocol was put in place following REC and HPRA approval. Inclusion criteria for the initial Trial Protocol required that participants had <math>\geq 3</math> depressive episodes in 2 years for recruitment to the monitoring phase, in order to enrich the sample to achieve a highly recurrent population. This set eligibility at a higher threshold than the standardised DSM IV criteria for recurrent depressive disorder. In 2016, it became apparent that a low percentage of those screened were eligible to take part in the monitoring phase (2.5%), restricting the number of participants who could be randomised after the monitoring phase. A new criterion was proposed and approved: Eligibility of people with recurrent depressive disorder to be amended from <math>\geq 3</math> episodes including the instant depressive episode within two years, to <math>\geq 2</math> episodes including the instant episode within 2 years.</p> <ul style="list-style-type: none"><li>• Discussed by DMC, TSC (May 2016)</li><li>• Approved by Mater Hospitals REC (Aug 2016)</li><li>• Approved by HPRA (Oct 2016)</li><li>• Approved by SPMHS (site) REC (Nov 2016)</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 November 2016	Recruitment commenced Dec 2015 and was paused in Nov 2016 due to staff unavailability due to grant contract difficulties, resolved in April 2017. Researchers commenced employment May 2017 and recruitment recommenced May 16th, 2017.	16 May 2017

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This pilot trial was not designed to assess efficacy and due to low participant numbers, analysis by group is not appropriate. Descriptive statistics are therefore used throughout. The primary outcomes are feasibility outcomes.

Notes: