Clinical trial results:
Ketamine as an adjunctive therapy for Major Depression - a randomised controlled pilot trial: The KARMA-Dep Trial

Summary

EudraCT number	2016-004764-18
Trial protocol	IE
Global end of trial date	21 September 2018

Results information

Result version number	v1 (current)
This version publication date	21 December 2020
First version publication date	21 December 2020

Trial information

Trial identification

Sponsor protocol code	01-17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03256162
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	St Patrick's Mental Health Services
Sponsor organisation address	James Street, Dublin, Ireland,
Public contact	Bronagh Gallagher, St Patrick’s Mental Health Services, 00353 12493385, bgallag@tcd.ie
Scientific contact	Bronagh Gallagher, St Patrick’s Mental Health Services, 00353 12493385, bgallag@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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2018
Global end of trial reached?	Yes
Global end of trial date	21 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study was to conduct a pragmatic randomised controlled patient- and rater-blinded pilot trial of a four-week course of once-weekly infusions of ketamine compared to midazolam as an adjunctive therapy for depression. The main objective of this pilot trial was to assess trial procedures to inform a future definitive trial, including rates of recruitment, dropout and completion of follow-up assessments.

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 including medication changes and multi-disciplinary team input.

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 rapid antidepressant effect 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 an adjunctive treatment in depressive episode. 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	06 September 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	19
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients who were admitted to St Patrick's University Hospital for treatment of a depressive episode between September 2017 and June 2018 and who met eligibility criteria for the trial were approached by the research team within 10 days of admission.

Pre-assignment

Screening details:

Clinical notes of newly admitted patients were screened for exclusion criteria. Eligible patients were then approached by the research team and baseline assessments were completed.

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:

Block randomisation was performed by another researcher within St Patrick's University Hospital and who was not otherwise associated with the Karma-Dep pilot trial. Randomisation was done in blocks of two and four.

Arms

Are arms mutually exclusive?	Yes
Arm title	ketamine

Arm description:

Consented participants were randomly allocated to a four-week course of either once-weekly ketamine (0.5mg/kg) or midazolam (0.045mg/kg) infusions given over 40 minutes and with 12 weeks follow-up.

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:

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.

Arm title	midazolam

Arm description:

Consented participants were randomly allocated to a four-week course of either once-weekly ketamine (0.5mg/kg) or midazolam (0.045mg/kg) infusions given over 40 minutes and with 12 weeks follow-up.

Arm type	Active comparator
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:

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.

Number of subjects in period 1	ketamine	midazolam
Started	13	12
Completed	8	8
Not completed	5	4
Consent withdrawn by subject	3	3
Adverse event, non-fatal	2	1

Baseline characteristics

Reporting groups	
Reporting group title	ketamine
Reporting group description:	
Consented participants were randomly allocated to a four-week course of either once-weekly ketamine (0.5mg/kg) or midazolam (0.045mg/kg) infusions given over 40 minutes and with 12 weeks follow-up.	
Reporting group title	midazolam
Reporting group description:	
Consented participants were randomly allocated to a four-week course of either once-weekly ketamine (0.5mg/kg) or midazolam (0.045mg/kg) infusions given over 40 minutes and with 12 weeks follow-up.	

Reporting group values	ketamine	midazolam	Total
Number of subjects	13	12	25
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
geometric mean	48.8	52.3	
standard deviation	± 13.1	± 12.5	-
Gender categorical			
Units: Subjects			
Female	8	5	13
Male	5	7	12

End points

End points reporting groups

Reporting group title	ketamine

Reporting group description:

Consented participants were randomly allocated to a four-week course of either once-weekly ketamine (0.5mg/kg) or midazolam (0.045mg/kg) infusions given over 40 minutes and with 12 weeks follow-up.

Reporting group title	midazolam

Reporting group description:

Consented participants were randomly allocated to a four-week course of either once-weekly ketamine (0.5mg/kg) or midazolam (0.045mg/kg) infusions given over 40 minutes and with 12 weeks follow-up.

Primary: Adherence

End point title	Adherence[1]

End point description:

A total of 16 participants (64%) completed all four infusions, eight in each group.

End point type	Primary

End point timeframe:

Recruitment took place over a nine-month period between September 2017 and June 2018 and follow-up assessments were completed by September 2018.

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: As this is a pilot trial, it is not adequately powered to detect statistically significant differences between the two groups.

End point values	ketamine	midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: participants	8	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire trial

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	ketamine

Reporting group description:

Participants were randomly allocated to four once-weekly ketamine infusions (0.5 mg/kg over 40 minutes) compared to midazolam infusions (0.045 mg/kg over 40 minutes) as an adjunctive therapy in hospitalised depression.

Reporting group title	midazolam

Reporting group description:

Participants were randomly allocated to four once-weekly ketamine infusions (0.5 mg/kg over 40 minutes) compared to midazolam infusions (0.045 mg/kg over 40 minutes) as an adjunctive therapy in hospitalised depression.

Serious adverse events	ketamine	midazolam	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (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: 5 %

Non-serious adverse events	ketamine	midazolam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	1 / 12 (8.33%)	
General disorders and administration site conditions			
Nightmare	Additional description: One participant experienced nightmares during the infusion period		
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Dissociation	Additional description: Two participants experienced dissociation side-effects which were unpleasant		

subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2	0 / 12 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

As this is a pilot trial, it is not adequately powered to detect statistically significant differences between the depression scores of the two groups.

Notes: