Clinical trial results:
Ketamine as an adjunctive therapy for Major Depression (2) - a randomised controlled trial

Summary

EudraCT number	2019-003109-92
Trial protocol	IE
Global end of trial date	12 August 2024

Results information

Result version number	v1 (current)
This version publication date	16 August 2025
First version publication date	16 August 2025

Trial information

Trial identification

Sponsor protocol code	CRFSPN004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04939649
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Trinity College Dublin
Sponsor organisation address	College Green, Dublin, Ireland,
Public contact	Sponsor Project and Quality Manager, Trinity College Dublin, 00353 14103900, clinicaltrialsponsorship@tcd.ie
Scientific contact	Sponsor Project and Quality Manager, Trinity College Dublin, 00353 14103900, clinicaltrialsponsorship@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	11 July 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 April 2024
Global end of trial reached?	Yes
Global end of trial date	12 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To conduct a pragmatic randomised controlled patient- and rater-blinded trial of repeated adjunctive twice-weekly ketamine vs. midazolam infusions over four-weeks for patients hospitalised for severe depression and assess the MADRS score difference between arms from before the first infusion to 24 hours after the final infusion, supplemented by a 95% confidence interval. There will also be a 24 week follow-up.

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	43

From 65 to 84 years	17
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	62
Number of subjects completed	62

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ketamine

Arm description: -

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

Dosage and administration details:

The investigational medicinal product (IMP) is ketamine (Ketalar 10 mg/ml Solution for Injection/Infusion, Pfizer Ireland; 0.5 mg/kg of body weight)

Arm title	Midazolam

Arm description: -

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

Dosage and administration details:

Midazolam (Hypnovel 10 mg/5ml solution for injection, Roche Pharmaceuticals Ireland; 0.045 mg/kg of body weight)

Number of subjects in period 1	Ketamine	Midazolam
Started	32	30
Completed	32	30

Baseline characteristics

Reporting groups	
Reporting group title	Ketamine
Reporting group description: -	
Reporting group title	Midazolam
Reporting group description: -	

Reporting group values	Ketamine	Midazolam	Total
Number of subjects	32	30	62
Age categorical Units: Subjects			
Adults (18-64 years)	21	22	43
From 65-84 years	11	6	17
85 years and over	0	2	2
Age continuous Units: years			
arithmetic mean	54.3	52.7	
standard deviation	± 18.2	± 19.2	-
Gender categorical Units: Subjects			
Female	13	12	25
Male	19	18	37

End points

End points reporting groups	
Reporting group title	Ketamine
Reporting group description: -	
Reporting group title	Midazolam
Reporting group description: -	

Primary: MADRS	
End point title	MADRS
End point description:	
End point type	Primary
End point timeframe: +24 hr after final infusion	

End point values	Ketamine	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	30		
Units: points				
arithmetic mean (standard deviation)	15.44 (± 12.04)	17.43 (± 10.47)		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Ketamine v Midazolam
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.245
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening Visit 0 to final Visit 11 (24-week follow-up)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27

Reporting groups

Reporting group title	Ketamine
Reporting group description: -	
Reporting group title	Midazolam

Reporting group description: -

Serious adverse events	Ketamine	Midazolam	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 32 (21.88%)	5 / 30 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 32 (3.13%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Analgesic therapy			

subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal mass			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 32 (3.13%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self-injurious ideation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	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	29 / 32 (90.63%)	28 / 30 (93.33%)	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	4 / 32 (12.50%)	4 / 30 (13.33%)	
occurrences (all)	5	7	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	12 / 32 (37.50%)	13 / 30 (43.33%)	
occurrences (all)	19	37	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	3 / 32 (9.38%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	9 / 32 (28.13%)	16 / 30 (53.33%)	
occurrences (all)	12	25	
Investigations			
Investigations			
subjects affected / exposed	15 / 32 (46.88%)	14 / 30 (46.67%)	
occurrences (all)	27	36	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	1 / 32 (3.13%)	1 / 30 (3.33%)	
occurrences (all)	2	2	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	5 / 32 (15.63%)	7 / 30 (23.33%)	
occurrences (all)	7	15	

Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	 15 / 32 (46.88%) 29	 12 / 30 (40.00%) 32	
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1	 3 / 30 (10.00%) 3	
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1	 2 / 30 (6.67%) 2	
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	 12 / 32 (37.50%) 16	 2 / 30 (6.67%) 3	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	 4 / 32 (12.50%) 5	 2 / 30 (6.67%) 3	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	 2 / 32 (6.25%) 2	 0 / 30 (0.00%) 0	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	 5 / 32 (15.63%) 5	 6 / 30 (20.00%) 7	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	 4 / 32 (12.50%) 6	 1 / 30 (3.33%) 1	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 2	 1 / 30 (3.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2019	The primary objective was updated and clarified in the synopsis and section 10.1 to include the wording "and assess the mood-rating score difference between arms from before the first infusion to 24 hours after the final infusion, supplemented by a 95% confidence interval. There will also be a 24-week follow-up after the final infusion session." The Exclusion criteria was updated in the synopsis and section 11.2.3 to include "Currently taking any of the contraindicated medications listed in section 12.7.2" The period of clinical supervision was updated to be consistent throughout the protocol to include "from the beginning of the infusion" in sections 9.2.2, 11.3, 11.3.2.5, 11.3.4, 11.3.9 and section 11.5.
06 March 2020	Pharmacovigilance contact information has been updated throughout the protocol from CRF-UCC to SJH-CRF Observer's Assessment of Alertness/Sedation Scale - Responsiveness Subscale included in assessments section 11.3 and 11.3.4
02 September 2020	Correction of error to clarify that Concomitant medications two months prior to visit 0 will be documented. Section 11.2.1 and 11.3.9 updated to include; "Where possible, patients taking any regular benzodiazepines (every day for the past five days) should omit their dose on the morning of infusion sessions (see section 12.7.1). It is appreciated that omission of benzodiazepines may not be possible for all patients. This will be as per the Investigators discretion and documented in the patient notes". Section 12.7.1 updated to include: "However where possible, patients taking any benzodiazepines should omit their dose on the morning of infusion sessions. As per the SmPc for Ketalar, Diazepam is known to increase the half life of ketamine and prolongs its pharmacodynamic effects. Concurrent use of diazepam or other benzodiazepines will increase plasma levels and reduce the clearance rate of ketamine. Section 11.3.1 and 11.3.10.2 updated to include sponsor e-mail address clinicaltrialsponsorship@tcd.ie Table 1 Schedule of Assessments updated to include, fasting >6 hours before dosing and the omission of diazepines on the morning of dosing. Sections 9.2.2, 11.3.9 and 11.4 updated to include video conference instead of home visits. Section 13.2.2 updated to include Unlikely related: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

03 August 2022	• updated to clarify that participants will receive a course of up to eight infusions over four weeks • updated to include fasting for at least 3 hours before dosing but should take their cardiovascular medications with a sip of water. This has been reduced from six to three hours for patient comfort. Patients are not undergoing general anaesthesia, hence a prolonged fasting time is unnecessary. • updated to clarify that scores relating to sleep, appetite and medication adherence are carried over during visits. These include items 4 and 5 on the MADRS, and items 1,2,3,4,6,7,8,9 & 17 on the QIDS-SR. These scores will be carried over from -40 minutes before each infusion to +60 minutes, +120 minutes, and +24 hours after each infusion. • Not all patients have an ECG done on admission. For logistical reasons, timing of pre-infusion ECG has been extended to include period from admission up to first infusion and review by the trial anaesthetist. • To minimise patient burden, we are removing the NART assessment from the protocol as it is not essential. • Clarification of exclusion criteria regarding comorbid Axis 1 diagnoses. • We have broadened the time for completion of pre-infusion MADRS (-40 +/- 20 mins) to facilitate clinic logistics. • We have clarified exclusion criteria to be in line with SmPC's for both ketamine and midazolam. Patients can be randomised to either midazolam or ketamine. Bradycardia is a known adverse effect of midazolam and ketamine. Therefore, patients with pre-existing bradycardia will be excluded. • We have removed "or 20% increase" referring to blood pressure increase lasting more than 15 minutes that would render a patient ineligible to continue in the trial. People with low-normal blood pressure can have a 20% increase yet still be within the normal range of blood pressure. • corrected collection of concomitant medication at Visit 0 from two months prior to baseline to one month
10 October 2022	• Sections 7 and 11.2.3. Exclusion criteria with regards to psychiatric comorbidities have been clarified and amended to bring in line with recent major ketamine trials. • Data entry procedure has been changed from single to double entry to help minimise data entry errors.
17 May 2023	• Typographical and grammatical errors have been corrected throughout the text. • The former name (NUIG) for the University of Galway has been replaced with the new name throughout the text. • The millilitre amount of intravenous fluid has been removed throughout the text since the amount of fluid infused depends on the IMP and the weight of the patient. • In Section 17, data retention period has been updated to 25 years in accordance with Clinical Trial Regulation (CTR) (EU Regulation 536/2014) as this trial will soon be transitioning to CTR. • Statistical analysis plan in Sections 7 and 14 have been updated in line with the Statistical Analysis Plan V2.0 approved by the Data Monitoring Committee and the Trial Steering Committee. • In Section 11.3.2.3 and Table 1, the CTQ and the SAPAS have been removed to reduce participant burden as they are non-essential and the study will be underpowered for these analyses. • In Sections 7 and 10.3, exploratory objective 6 has been removed as the study will be underpowered to address this research question. • The descriptive term "severe" depression has been removed throughout the text to make the text consistent with the MADRS rating scale cut-off of 20 for entry which technically also includes moderate depression. • Concomitant medications are recorded primarily for safety reasons before and during the randomised treatment period (Visits 0-8). To ensure accuracy and full visibility to the monitoring staff, medications for Visits 0-8 are now being exported directly from the participant's electronic health record instead of manually recorded on a handwritten medication log. At long-term follow-up (Visits 9, 10 and 11), concomitant medications will continue to be recorded on another scale (CSRI). To avoid duplication, the concomitant medication log is no longer recording medications at these long-term follow-up timepoints. This has been clarified in Section 11.3.2.9. and Table 1.

17 May 2023	• There is no item 17 on the QIDS-SR16. This error has been rectified throughout the text. • It has been clarified in Table 1 footer that BMI is a derived variable from height and weight which are recorded variables. • In Section 11.3.2.1. and Table 1, the assessment of treatment-resistant depression has been simplified from the dimensional Maudsley Staging Method (MSM) to the categorical Antidepressant Treatment Response Questionnaire (ATRQ). This is to bring the methodology of the trial in line with other major trials in this area. There is no additional participant burden with the change from MSM to ATRQ since all the necessary information to rate the ATRQ has already been collected for all existing participants as part of the MSM. • In Section 9.2.2., it has been clarified that "low" doses refer to subanaesthetic doses. • In Section 11.3.4. (iv), recent references have been added to support the statement that there is no evidence of a withdrawal syndrome in the published ketamine literature to date. The risk of withdrawal remains a theoretical concern. The literature on ketamine safety is monitored on an ongoing basis by the investigators. Should any new concerns arise in the future, the Protocol and the PIL will be updated as appropriate. • In Section 11.3.6., the term "Withdrawal eCRF" was replaced with the correct term "End of Study Form". • In Section 13.2.5., the location of the displaying of the Emergency unblinding procedure has been updated. • In Section 16.1., it has been clarified that information exported from the electronic health record cannot be pseudonymised. These data are filed separately from the pseudonymised source data documents.
17 May 2023	• It has been clarified throughout the text that AEs are followed up until resolution or final visit. • Section 23 has been updated to remove the section about trial newsletter. • The role of the sponsor in publication activities was removed in Section 23. • The Department of Psychiatry, Trinity College Dublin affiliation has been added to Section 23 • The definition of relapse (Section 11.3.3) has been updated to bring in line with recent major trials of antidepressants in relapse prevention.
12 October 2023	• It has been clarified throughout the document that depression can be "moderate or severe" at trial entry. • Population figure for Ireland has been updated with a 2023 estimate on Page 17.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported