



Clinical trial results:

The clinical effectiveness and cost effectiveness of clozapine for inpatients with borderline personality disorder: randomised controlled trial

Summary

EudraCT number	2018-002471-18
Trial protocol	GB
Global end of trial date	22 July 2021

Results information

Result version number	v1 (current)
This version publication date	18 April 2022
First version publication date	18 April 2022

Trial information

Trial identification

Sponsor protocol code	CALMED v9.0
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Additional study identifiers

ISRCTN number	ISRCTN18352058
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	Mike Crawford, Imperial College London, 44 2083834161, m.crawford@imperial.ac.uk
Scientific contact	Mike Crawford, Imperial College London, 44 2083834161, m.crawford@imperial.ac.uk

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	04 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2021
Global end of trial reached?	Yes
Global end of trial date	22 July 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

For people receiving inpatient treatment for borderline personality disorder who have not responded well to usual care (including at least three months taking another antipsychotic drug), to determine whether the addition of clozapine to their usual care lead to improved mental health six months later, compared to adding a placebo to their usual care?

Protection of trial subjects:

Thorough monitoring of adverse events and participant wellbeing occurred as part of the assessment process. During assessment and testing breaks were provided to minimise possible fatigue or stress, and if indicated, the assessment were spread over more than one visit. We and others including independent oversight committees regularly appraised the study, including undertaking a review of known safety information about clozapine. Where necessary changes were made to the protocol in response to this oversight.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 29
Worldwide total number of subjects	29
EEA total number of subjects	0

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)	29

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited via NHS organisations in England from 11 Sept 2019 to 04 March 2021.

Pre-assignment

Screening details:

Excluded if a) Current diagnosis of schizophrenia/bipolar I; b) Prescribed clozapine in previous 2 weeks; c) pregnant, trying to conceive, breastfeeding, not using birth control; d) Contraindication to clozapine; e) Due to be discharged within 2 weeks; f) unable to speak English; g) lacks capacity to consent; h) unable to have regular blood tests

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, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	clozapine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	clozapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A flexible dosing regimen with dosing starting with 12.5 mg once daily and titrated to 300mg over a 15-day period. Study participants may be prescribed a dose of up to 400mg of clozapine daily, depending on clinical response, patient preference and side effects. The dose could be maintained at or reduced to a lower dose at any time.

Arm title	placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A flexible dosing regimen of placebo as if clozapine. Dosing started with one capsule once daily and was titrated to four capsules over a 15-day period. Study participants could be prescribed a dose of capsules up to that comparable to 400mg of clozapine daily, depending on clinical response, patient preference and side effects. The dose could be maintained at or reduced to a lower dose at any time.

Number of subjects in period 1	clozapine	placebo
Started	15	14
Completed	14	10
Not completed	1	4
Lost to follow-up	1	4

Baseline characteristics

Reporting groups

Reporting group title	clozapine
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Reporting group values	clozapine	placebo	Total
Number of subjects	15	14	29
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	28 ± 7.54	33 ± 11.25	-
Gender categorical Units: Subjects			
Female	11	11	22
Male	4	3	7
ZAN-BPD baseline Units: scale score arithmetic mean standard deviation	20.9 ± 7.21	18.8 ± 6.93	-

End points

End points reporting groups

Reporting group title	clozapine
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Primary: ZAN-BPD

End point title	ZAN-BPD ^[1]
End point description: Scores adjusted for baseline, allocation group and site.	
End point type	Primary
End point timeframe: six month follow up	

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: Statistical analysis is not presented due to the small sample of participants recruited and followed up. Any analysis on such small numbers would lack statistical power and be inappropriate to present.

End point values	clozapine	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: scale score				
arithmetic mean (standard deviation)	9.7 (± 2.38)	13.5 (± 2.92)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

There were participants in the trial between 11 Sept 2019 and 22 Sept 2021

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	clozapine
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Reporting group description: -

Reporting group title	placebo
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Reporting group description: -

Serious adverse events	clozapine	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	4 / 11 (36.36%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			

subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional self-injury			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	clozapine	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)	6 / 11 (54.55%)	
Vascular disorders			
Varicose vein			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Cerumen removal			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all) Chest discomfort subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Hyperthermia subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all)	1 / 15 (6.67%)	0 / 11 (0.00%)	
	1	0	
	1 / 15 (6.67%)	0 / 11 (0.00%)	
	1	0	
	2 / 15 (13.33%)	1 / 11 (9.09%)	
	2	1	
	3 / 15 (20.00%)	0 / 11 (0.00%)	
	3	0	
	1 / 15 (6.67%)	0 / 11 (0.00%)	
	3	0	
	2 / 15 (13.33%)	0 / 11 (0.00%)	
	2	0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hypoxia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

Anger		
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	3
Anxiety		
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)
occurrences (all)	1	1
Disorientation		
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)
occurrences (all)	1	0
Drug withdrawal syndrome		
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)
occurrences (all)	2	0
Emotional distress		
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)
occurrences (all)	1	0
Fear of weight gain		
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)
occurrences (all)	1	0
Hallucination, auditory		
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	1
Head banging		
subjects affected / exposed	2 / 15 (13.33%)	1 / 11 (9.09%)
occurrences (all)	2	1
Intentional overdose		
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)
occurrences (all)	1	0
Intentional self-injury		
subjects affected / exposed	5 / 15 (33.33%)	5 / 11 (45.45%)
occurrences (all)	27	13
Paranoia		
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)
occurrences (all)	1	0
Psychogenic seizure		
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)
occurrences (all)	1	0

Somnolence subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Suicidal behaviour subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Suicidal ideation subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2	0 / 11 (0.00%) 0	
Troponin T increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 11 (9.09%) 1	
Weight increased subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3	0 / 11 (0.00%) 0	
Injury, poisoning and procedural complications Accidental overdose subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Fall subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Frostbite subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Head injury subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Tooth injury subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	4 / 15 (26.67%)	1 / 11 (9.09%)	
occurrences (all)	9	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 15 (13.33%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Headache			
subjects affected / exposed	2 / 15 (13.33%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Lethargy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	3 / 15 (20.00%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Tremor			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Excessive cerumen production			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Gastrointestinal disorders			

Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 4	0 / 11 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	1 / 11 (9.09%) 2	
Dysphagia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 11 (9.09%) 1	
Salivary hypersecretion subjects affected / exposed occurrences (all)	6 / 15 (40.00%) 6	0 / 11 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	1 / 11 (9.09%) 1	
Skin and subcutaneous tissue disorders			
Eczema subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 11 (9.09%) 1	
Rash subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Renal and urinary disorders			
Incontinence subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	2 / 11 (18.18%) 2	

Back pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Groin pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Infections and infestations			
Tooth abscess			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Abnormal weight gain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Dehydration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2019	Changes to protocol, PIS (addition of payment at baseline) Capsule size changed
17 December 2019	Addition of an eligibility criterion to include only those with severe personality disorder and how that is defined Addition of the assessment SAS-PD at six-month follow-up Update to the table showing summary of known risks of clozapine to reflect most currently approved RSI in sIMPD v2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	The trial halted recruitment on 17th March due to the COVID-19 pandemic.	08 July 2020

Notes:

Limitations and caveats

None reported