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The purpose of the trial is to test the safety, tolerability and efficacy of the drug tildacerfont, that is being developed for the treatment of major depressive disorder

Submission date
28/03/2025

Recruitment status
Recruiting

Registration date
08/05/2025

Overall study status
Ongoing

Last Edited
08/05/2025

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The purpose of this study is to test the drug tildacerfont, which is being developed for the treatment of Major Depressive Disorder (MDD). MDD is a highly debilitating mental disorder, ranked as one of the leading causes of disability worldwide by the World Health Organisation. Many people do not gain sufficient benefit or suffer side effects from the current approved medications. The current antidepressant pharmaceutical therapies, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants, have several limitations. There is an unmet need for novel treatments that offer better clinical outcomes by adequately addressing the underlying biology of depression. Increasing attention is drawn to the field of precision psychiatry, which aspires to provide personalised treatments for patients, after accounting for their biological variabilities. The aim is to allocate patients to treatments they are most likely to benefit from, by accurately characterising their genetics, neuronal circuits and other physiological parameters. This study will evaluate the use of tildacerfont for depression in people with a positive CRHR1CDx result, which the Sponsor believes reflects a predisposition for altered stress regulation.

Who can participate?
Patients aged 18-65 years with moderate to severe depression who are not currently taking antidepressant medication or are willing to discontinue them

What does the study involve?
Participants will be divided into two groups; one group will be administered doses of tildacerfont, and one group will be administered a placebo. There is an equal chance of getting either medication or a placebo. Participation in the study will last 15 weeks, and participants will be required to attend eight study visits, consisting of one screening visit and seven clinic visits. Participants will also be contacted by phone on one occasion. Study visits will take place at UK clinical research units.

What are the possible benefits and risks of participating?
As is common with blood drawing, participants may feel some discomfort when the needle goes into the vein. In addition, participants may experience lightheadedness or irritation, such as redness, tenderness and bruising at the sites used to obtain blood. Blood tests can also make participants feel faint, so they will be asked to lie down when the blood is drawn. The swelling of a vein, or in very rare cases, a blood clot, cannot be entirely ruled out. Infection is rare but could occur. An ECG is a safe test. Participants may experience local skin irritations and redness from the stickers on their skin, which will recover quickly.

Where is the study run from?
MAC Clinical Research (UK)

When is the study starting and how long is it expected to run for?
March 2025 to May 2026

Who is funding the study?
HMNC Holding GmbH (Germany)

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1012061

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
BH-400-01

Study information

Scientific Title
A 15-week, multi-centre, double-blind, randomised, placebo-controlled Phase II proof-of-concept trial with an 8-week treatment period to study the safety, tolerability and efficacy of a fixed dose of tildacerfont in outpatients with major depressive disorder

Study objectives
The primary objective of the trial is to explore the efficacy of tildacerfont versus placebo in improving depressive symptoms in CRHR1CDx-positive participants with MDD.

The CRHR1CDx is a qualitative, non-automated, next-generation sequencing-based in vitro diagnostic device intended for use by healthcare professionals for patients with Major Depressive Disorder (MDD).

Secondary objectives:
1. To explore the efficacy of tildacerfont versus placebo on response rate, remission rate, and quality of life in CRHR1 CDx-positive participants with MDD.
2. To explore the overall safety and tolerability of tildacerfont versus placebo in CRHR1CDx-positive participants with MDD.
3. To explore plasma concentrations of tildacerfont.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Pending approval, South Central Oxford A, ref: 25/SC/0104

Study design
15-week multi-centre double-blind randomized placebo-controlled Phase II proof-of-concept trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Home, Hospital, Medical and other records, Telephone

Study type(s)
Safety, Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Major depressive disorder (MDD)

Interventions
There are two treatment arms in this double-blinded study. Participants will take either tildacerfont (the study drug) or placebo. At least 88 participants will take part in this study. Half of the participants will receive the study drug, and half will receive placebo. It will be randomly determined (by chance) which treatment participants will be assigned to. There is a 1 in 2 (50%) chance of receiving the study drug and a 1 in 2 (50%) chance of receiving the placebo. Participants' participation in the study will last up to approximately 15 weeks and they will self-administer the study medication orally twice daily for 8 weeks. This is a fixed-dose study with no scheduled dose adjustment. Participants will be required to attend the clinic for study visits on eight occasions in total, consisting of a screening visit, six visits during the 'Treatment Period' (Day 0, Day 7, Day 14, Day 28, Day 42 and Day 56), and a follow-up visit on Day 84.

Participants will be randomised via a MAC Clinical Research Standard Operating Procedure when eligibility is confirmed. This is a manual process that uses an electronic randomisation list. Sealed Code break envelopes will be provided to all sites ahead of randomisation and stored appropriately.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacokinetic, Pharmacogenetic, Pharmacogenomic

Phase
Phase II

Drug/device/biological/vaccine name(s)
Tildacerfont

Primary outcome measure
Depression measured using the Hamilton Depression Rating Scale (HAMD-17) total score at baseline, and days 7, 14, 28, and 42

Secondary outcome measures
Key secondary endpoint:
Functional Impairment is measured using the Sheehan Disability Scale (SDS) from baseline to Day 56

Further secondary endpoints will be assessed at baseline and each post-baseline visit, except where stated:
1. The severity of depressive symptoms is measured using the HAMD-17 total score
2. The severity of depression symptoms is measured using the 6-item HAMD (HAMD-6) total score
3. The severity of depression symptoms is measured using the Montgomery-Åsberg Depression Rating Scale (MADRS)
4. The severity of depression symptoms is measured using the 6-item MADRS (MADRS-6) total score
5. Response rate is measured using the HAMD-17 total score, response is defined as an at least 50% reduction in the total score of HAMD-17 compared with baseline
6. Remission rate is measured using HAMD-17 total score, remission is defined as total HAMD-17 score ≤7
7. Response rate is measured using total MADRS score, response is defined as at least a 50% reduction in the total score of MADRS compared with baseline
8. Remission rate is measured using the total MADRS score, remission is defined as the total MADRS score ≤10
9. Severity of depression is measured using the Patient Health Questionnaire-9 (PHQ-9)
10. Severity of symptoms measured using the Clinical Global Impression Scale – Severity (CGI-S)
11. Functional Impairment is measured using the Sheehan Disability Scale (SDS)
12. Health-related quality of life measured using the 5-level EQ-5D (EQ-5D-5L)
13. The number of reported adverse events (AEs) and serious adverse events (SAEs) measured using data collected from case report forms, and the number of reported clinical safety abnormalities measured using clinical laboratory evaluations and ECG
14. Plasma concentrations of tildacerfont measured using Plasma PK blood tests on days 7, 28 and 56

Overall study start date
24/03/2025

Completion date
28/05/2026

Eligibility

Key inclusion criteria
1. Able to comprehend and willing to sign an ICF and to comply with all aspects of the trial
2. Male or female
3. Aged between 18 to 65 years (inclusive) at the date of informed consent
4. Body mass index (BMI) of 18 to 35 kg/m2, inclusive
5. CRHR1CDx-positive
6. Outpatients
7. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) diagnostic criteria for MDD (moderate or severe, single or recurrent episode, with or without psychotic features [International Classification of Diseases (ICD)-10-CM codes F32.1, F32.

2, F32.3, F33.1, F33.2, F33.3]), confirmed by the Mini-International Neuropsychiatric Interview (MINI). Participants with the following co morbid conditions can be included (secondary diagnosis), as long as the primary diagnosis is MDD:
7.1. Anxiety disorders, e.g. generalised anxiety disorder (GAD) or panic disorder
7.2. Post-traumatic stress disorder (PTSD)
7.3. Obsessive-compulsive disorder (OCD), if the current episode is not impairing/disabling or interfering with the participant's adherence to trial medication intake and the trial protocol
7.4. Eating disorders, if the condition does not impact the efficacy of the trial medication or raise safety concerns in the Investigator's opinion
7.5. Attention deficit hyperactivity disorder (ADHD), if the participant is able to maintain adequate levels of concentration to consent to the trial and undergo the trial assessments, and does not require pharmacological intervention
8. MADRS score ≥25 at screening and baseline
9. Duration of current episode no longer than 12 months prior to screening
10. Symptoms of depression present for at least 2 weeks prior to screening
11. Willingness to stop prohibited psychotropic medication at least 7 days or 5 half-lives, whichever is longer, before baseline (Visit 2). When needed as sleeping or anti-anxiety medication, selected benzodiazepines and non-benzodiazepines are permitted as specified in Appendix 3
12. Male participants must use a condom during the trial from screening until 90 days after their final dose of trial medication, if their partner is a female of childbearing potential. In addition, their partner of childbearing potential must use an additional method of highly effective contraception (see Section 6.3.1 for highly effective methods of contraception) from screening until 90 days following final dosing
Note: Throughout this Protocol, the use of male/female refers to the biological gender assigned at birth.
Note: If the male participant or partner is vasectomised (and the absence of sperm has been confirmed) then this will be accepted as a form of highly effective contraception, in addition to the male also wearing a condom
13. Female participants:
13.1. Of childbearing potential must agree to use a highly effective method of contraception (see Section 6.3.1 for highly effective methods of contraception) in combination with their male partner's use of a condom from screening until 30 days after their final dose of trial medication. Participants must have a negative pregnancy test at Visit 1 and Visit 2.
13.2. Of nonchildbearing potential (i.e., postmenopausal or permanently sterile following hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy). A postmenopausal state is defined as spontaneous amenorrhoea for at least 12 months without an alternative cause, and a serum FSH level within the menopausal range (≥40 mIU/mL), unless the participant is taking hormone replacement therapy (HRT) or is using hormonal contraception. Participants who are taking HRT (at a stable dose with no intention of dose adjustment during the trial) can continue to do so during the trial, but they must also use a highly effective method of contraception.
14. Psychotherapy that has been ongoing for a minimum of 6 weeks prior to screening can continue, but new psychotherapy may not be initiated from 6 weeks prior to screening until after final dosing. Discontinuation of ongoing psychotherapy during the trial should be avoided until after final dosing.
15. Physical activity programs designed to alleviate symptoms of depression that have been ongoing for a minimum of 6 weeks prior to screening can continue but should be kept on the same level (i.e., type and frequency). New physical activity programs designed to alleviate symptoms of depression may not be initiated from 6 weeks prior to screening until after final dosing. Discontinuation of such ongoing physical activity programs during the trial should be avoided until after final dosing.
16. Ongoing hormone substitution therapy for post-menopausal women, insulin treatment for

diabetes and thyroid disorders is allowed as long as these conditions are well controlled (see exclusion criteria below). Only hormonal agents prescribed by healthcare providers are allowed.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
88

Key exclusion criteria
1. A CRHR1CDx-negative result
2. Currently ongoing psychiatric and neurological concomitant condition
3. Significant risk of suicide
4. Unable to complete or tolerate wash-out from current antidepressant medication (if applicable). Participants who are able to wash out but require a longer wash-out period that is not considered appropriate will be excluded
5. Wash-out of existing antidepressant medication (if applicable) is considered unsuitable for the participant (e.g., participant is receiving benefit from their existing antidepressant treatment in the opinion of the Investigator, or the risks of discontinuation outweigh the benefit of participating in the trial)
6. Known or suspected lifetime history of surgical procedures involving the brain or meninges, encephalitis, meningitis, degenerative CNS disorder, epilepsy or any other disease/procedure /accident/intervention
7. Known or suspected cardiovascular/cerebrovascular disease
8. Untreated hypertension and a systolic blood pressure >160 mmHg (at rest) and/or diastolic blood pressure >100 mmHg (at rest) at screening
9. Clinically relevant abnormal ECG findings at screening, including a QTcF ≥470 msec in females or ≥450 msec in males
10. Clinically relevant abnormal laboratory results, vital signs or physical findings at screening
11. A history of, or symptoms and signs suggestive of, impaired hepatic function or cirrhosis, including an ALT or AST value >2 × the ULN, and/or total bilirubin >1.5 × the ULN, and/or total bile acids >5 × the ULN, and/or a ratio of ALT: alkaline phosphatase (ALP) normalised to ULN for each ([ALT/ULNALT]/ [ALP/ULNALP] >5, at screening.
12. Positive test for hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (anti-HCV) or human immunodeficiency virus 1 and 2 (anti-HIV 1/2) at screening
13. Cushing’s Syndrome
14. Addison’s Disease
15. Renal insufficiency
16. Uncontrolled diabetes (glycated haemoglobin [HbA1c] >8.0% at screening) or diabetes

treatment ongoing for less than 3 months prior to screening
17. Known but untreated conditions causing hyperthyroidism or hypothyroidism, with the following
18. Hypopituitarism or bilateral adrenalectomy
19. Participants with any significant disease or disorder
20. A history of moderate to severe alcohol use and/or substance use disorder
21. A positive result on the urine drug screen for substances of abuse (Table 3) at screening
22. Intake of benzodiazepines during the trial is prohibited (see Appendix 3 for exceptions and restrictions)
23. A history of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation or any experimental CNS treatment during the current episode or within 6 months prior to screening
24. Donation or loss of whole blood ≥500 mL within 2 weeks prior to first dosing. Blood donation during the 8 weeks of IMP intake is prohibited
25. Participants who have received an IMP or used an invasive investigational medical device in a clinical trial, within 6 months prior to screening. Use of any investigational drugs (with the exception of tildacerfont) is prohibited during the trial
26. Participation in 2 or more clinical interventional trials within 1 year prior to screening
27. Current enrolment in a clinical interventional trial
28. Female participants of childbearing potential who are pregnant, breastfeeding or planning to conceive during the course of the trial and follow-up
29. Male participant who will not abstain from sperm donation from screening until at least 90 days after final dosing
30. Female participant who will not abstain from egg donation from screening until at least 30 days after final dosing
31. History or clinical evidence of any disease and/or existence of any surgical or medical condition which might interfere with the ADME of the trial medication
32. Personal or family history of sudden death/long QT syndrome
33. Any history of significant bleeding/haemorrhagic tendencies
34. History of severe adverse reactions or allergies, or history of an anaphylactic reaction to prescription or non-prescription medication or food (non-active hay-fever is acceptable)
35. Participants who routinely work overnight shifts
36. Employees of the Investigator, trial centre, Sponsor, clinical research organisation or trial consultants, when employees are directly involved in this trial or other studies under the direction of this Investigator or trial centre, and their family members
37. Persons committed to an institution by virtue of an order issued either by the judicial or other authorities.
38. Any antidepressant treatment
39. OTC medications and herbal extracts intended for the treatment of mood disorders
40. Use of hormonal agents prohibited
41. Cough/cold medications containing dextromethorphan
42. Current treatment with opioids/barbiturates
43. Strong inhibitors of CYP3A4
44. Intake of any sleep/anti-anxiety medication is prohibited within 24 hours before on-site visit
45. Systemic treatment with corticosteroids or other drugs with a potential effect on the HPA axis

Date of first enrolment
11/05/2025

Date of final enrolment

27/10/2025

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
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Sponsor type
Industry

Funder(s)

Funder type
Industry

Funder Name
HMNC Holding GmbH

Results and Publications

Publication and dissemination plan
Peer-reviewed scientific journals
Internal report
Conference presentation
Submission to regulatory authorities
Other

Intention to publish date
28/05/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available. Participants' records from the study are confidential unless law requires certain people to see them, such as the sponsor or representatives, monitors, auditors and regulatory agencies. Participants will be informed about this in the Patient Information Sheet and consent will be obtained. Participants will be allocated a subject number once they have signed the informed consent form. Anonymised data may be sent to the regulatory bodies and collaborators within the pharmaceutical industry. The study plans to report and disseminate the results of the study via peer-reviewed scientific journals, internal reports, conference presentations, submission to regulatory authorities, and a result summary will be provided on https://www.clinicaltrials.gov.

IPD sharing plan summary
Not expected to be made available