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A clinical study to investigate whether third-line treatments work better as a second-line treatment for people diagnosed with schizophrenia

Submission date
09/11/2023

Recruitment status
Recruiting

Registration date
27/03/2024

Overall study status
Ongoing

Last Edited
17/09/2024

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
When people with a psychotic disorder are diagnosed, treatment is initiated and usually an antipsychotic medication is started. Beforehand it is unknown if the medication will reduce symptoms and what side effects the medication causes. When the first-line treatments do not work sufficiently, it is currently unknown what medication works best as a second-line treatment. This study aims to investigate if the first treatment does not work sufficiently, and if it is better to use clozapine (generally used as a third-line treatment), instead of the second-line treatment. Third-line treatments are expected to be more effective, and it is expected that the side effects are similar when used as a second-line treatment.

Who can participate?
Patients aged 18 to 70 years with schizophrenia, schizoaffective disorder, or schizophreniform disorder

What does the study involve?
Not provided at time of registration

What are the possible benefits and risks of participating?
All medications as part of this study are widely used (alone or in combination) on a daily basis in clinical practice. In the current study, we mimic clinical practice as much as possible to maximise generalisability and study feasibility, meaning that SmPCs are followed with regard to contraindications (implemented in the exclusion criteria), precautions, dose modifications, safety measures and potential simultaneous use with other medication.
Overall, the risks are similar to daily clinical practice as the only difference between this study and clinical practice is that the early-intensified pharmacological treatment group receives the treatment earlier in their illness course. Clozapine has been used for decades in patients with schizophrenia and carries a well-known safety profile. There are no indications in existing literature that the earlier introduction of these medications poses a safety risk (section 2.2). The

study mimics clinical practice as much as possible; physicians will provide the same healthcare as they normally would when prescribing these medications. If the subject does develop side effects or takes an overdose, there are standard measures described in the SmPCs that can be taken to reduce/eliminate risks. When a patient is randomised, the SmPC will be discussed with the patient to ensure the patient is aware of the risks.
The only difference between clozapine (EIPT) and a second-line antipsychotic (TAU) is that for clozapine, most local guidelines demand weekly blood draws to check White Blood Cell Count /Absolute Neutrophil Count as too low values might indicate agranulocytosis or neutropenia, which could be dangerous if not detected in time. The overall risk for developing agranulocytosis /neutropenia is 3.8%. With the weekly blood draw the risk is significantly reduced. The burden of a blood draw is a hematoma/contusion which poses no safety risk. Thus, the additional burden is limited.
To ensure that participants have no or low suicidal ideation, the suicidality module of the Mini International Neuropsychiatric Interview (MINI) v7.0.2 is obtained, as treatment allocation through randomisation may not be the optimal treatment option for subjects with suicidal ideation. When participating in the study, the Childhood Trauma Questionnaire (CTQ) is obtained at visit 2, which could be perceived as uncomfortable (if a trauma is present). However, it is widely implemented in research and if participants want to stop completing this questionnaire, this is allowed. The potential side effects of all treatments are well-known and will be monitored during the study with a General Assessment of Side Effects (GASE), spontaneous adverse event reporting and the local standard procedure regarding other measures such as laboratory tests, physical examinations, and ECGs. The results will be captured in our dataset and reviewed by a physician. Most of the tests that will be conducted as part of standard clinical care (lab tests, ECG, physical examination) for EIPT are also part of TAU, as the side effect profiles are comparable. Finally, all safety data will be regularly reviewed by the project manager and Study Management Group, as well as in an annual Data Safety Monitoring Board meeting.
The hypothesis is that the early-intensified treatment is more efficacious for the participants. While ensuring that the tolerability and additional burden remain acceptable, the researchers expect that the larger effect on symptom severity will justify the slight increase in burden relative to the TAU group. When participants are treated with intense treatment in an earlier stage of the illness (less trial and error before moving on to this treatment option), this is expected to result in a reduced burden of disease for subjects, expressed as fewer relapses, lower all-cause death rate, hospitalisations and job losses and improved quality of life, in addition to lower societal and healthcare costs. This is already demonstrated in Therapy Resistant Schizophrenia (TRS). In conclusion, in the researchers' view, the potential benefits outweigh the risks.

Where is the study run from?
King's College London (UK)

When is the study starting and how long is it expected to run for?
November 2023 to August 2026

Who is funding the study?
Horizon 2020 Framework Programme (EU)

Who is the main contact?
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Contact information

Type(s)
Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1008551

ClinicalTrials.gov (NCT)
NCT05958875

Protocol serial number
2023-506602-39-00, IRAS 1008551

Study information

Scientific Title
A randomised, controlled trial to investigate the effect of a 6-week intensified pharmacological treatment for schizophrenia compared to treatment as usual in subjects who had a first-time treatment failure on their first-line treatment

Acronym
INTENSIFY - Schizophrenia

Study objectives
The primary objective is to compare the treatment response (baseline; visit 2 vs. end of treatment; visit 4), expressed as mean change in symptom severity as measured through the Positive And Negative Syndrome Scale (PANSS) under an early-intensified pharmacological treatment to that under treatment as usual, in subjects who had a first-time treatment failure on their first-line treatment for schizophrenia, schizoaffective or schizophreniform disorder.

1. Comparison of the proportion of participants (EIPT vs. TAU) in symptomatic remission at end of treatment (visit 4)

Between arms over 6-week treatment period:
1. Compare changes in PANSS sub-scale scores (positive, negative and general)

2. Compare changes in the severity and improvement sub-scores of the Clinical Global Impression Scale (CGI)
3. Compare changes in the levels of depression and anxiety as assessed with the Hospital Anxiety and Depression Scale (HADS)
4. Compare changes in cognitive performance
5. Compare changes in quality of life and functioning measures
6. Compare presence of side effects as measured through General Assessment of Side Effects Scale (GASE) and reported spontaneously
7. Compare use of concomitant medication
8. Compare premature discontinuation (timing and reason)

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 13/03/2024, East Midlands – Nottingham 2 REC (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8009; nottingham2.rec@hra.nhs.uk), ref: 23/EM/0266

Study design
Open randomized controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Schizophrenia, schizoaffective disorder or schizophreniform disorder

Interventions
Arm 1 - Experimental: Schizophrenia early intensified treatment (EIPT): When randomised to clozapine, they will receive clozapine for six weeks. Dose ranges and dose titrations as described in the latest applicable SmPCs are to be followed.
Arm 2 - Active Comparator: Schizophrenia treatment as usual (TAU): When randomised to TAU, they will receive any second-line antipsychotic for six weeks. The selection of treatment and the dosage per day is up to the investigator/treating physician’s judgement. All applicable information can be found in the most recent SmPCs.

Intervention Type
Drug

Phase
Phase IV

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

Primary outcome(s)
Symptom severity measured using the Positive and Negative Symptom Scale (PANSS) at baseline (visit 2) to end of treatment (visit 4)

Key secondary outcome(s))
1. The proportion of participants (EIPT versus TAU) that is in symptomatic remission at the end of treatment is measured at the end of the 6-week treatment period (visit 4). Remission is defined as meeting the PANSS modified Andreasen criteria: (Low scores (≤3) P1. Delusions; P3. Hallucinatory behaviour; P2. Conceptual disorganization; N1. Blunted affect; N4. Passive /apathetic social withdrawal; N6. Lack of spontaneity and flow of conversation; G5. Mannerisms /posturing; G9. Unusual thought content.)
2. Positive and Negative Symptom Scale (PANSS) subscale scores (positive, negative and general) between baseline (visit 2) and end of 6-week treatment period (visit 4)
3. Severity and improvement sub-scores of the Clinical Global Impression Scale (CGI) between baseline (visit 2) and end of 6-week treatment period (visit 4).
4. Depression and anxiety are measured using the Hospital Anxiety and Depression Scale (HADS) between baseline (visit 2) and end of the 6-week treatment period (visit 4).
5. Cognitive performance is measured using the Trail Making Test, Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test as well as the Perceived Deficits Questionnaire (PDQ) between the baseline (visit 2) and end of 6-week treatment period (visit 4)
6. Quality of life and functioning is measured using the Q-LES-Q-SF, LAPS, QLS-100, and SDS between baseline (visit 2) and end of 6-week treatment period (visit 4)
7. Side effects are measured using the General Assessment of Side Effects Scale (GASE) and reported spontaneously between baseline (visit 2) and end of 6-week treatment period (visit 4).
8. Use of concomitant medication is measured by participant reports between baseline (visit 2) and end of the 6-week treatment period (visit 4)
9. Premature discontinuation (timing and reason by participant report) is measured between baseline (visit 2) and end of 6-week treatment period (visit 4).

Completion date
30/08/2026

Eligibility

Key inclusion criteria
1. In- or out patients, at least 18 years of age up until 70 years
2. Being willing and able to provide written informed consent. If unable and allowed by local laws and regulations, having a legal guardian to provide written informed consent is allowed (subject's opinion will also be considered in these cases).
3. Female subjects of child bearing potential must use effective contraception during the trial as per the requirements of the applicable SmPCs and should have a negative pregnancy test at visit 1 (section 8.2 of protocol).
4. Meeting diagnostic criteria for a primary diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder, according to DSM-5. The primary diagnosis will be confirmed by the Mini International Neuropsychiatric Interview (MINI v7.0.2).
5. Subject currently experiences his/her first treatment failure due to lack of efficacy; this treatment is a first-line pharmacotherapeutic agent for the primary DSM-5 diagnosis, and was prescribed for at least 4 weeks within the dose range as specified in the Summary of Product Characteristics (SmPCs). *
6. Subject has failed on current psychopharmacological treatment of current episode of SZ, as confirmed by a CGI-I ≥3. **
7. Subject and clinician intend to change pharmacotherapeutic treatment. ***
8. A minimum symptom severity threshold needs to be present (moderate level; see below) and subject needs to experience functional impairment.

8.1. The minimum symptom severity threshold is at least 2 PANSS positive or negative items with a score of 4, or at least one PANSS positive or negative item with a score of 5.
8.2. Functional impairment is defined as a score of 5 or higher on any of the three scales of the Sheehan Disability Scale (SDS).

* If subjects already stopped the previous pharmacological treatment due to lack of efficacy, the stopped treatment should still be the first treatment failure on a first-line pharmacotherapeutic agent prescribed for at least 4 weeks within the dose range as specified in the SmPC.
** Preferably, the CGI-I is obtained from the (previous) treating physician or clinical team, who decided that there is a treatment failure. If this is not possible, it is accepted to obtain this information from the subject.
*** Change is considered a full change (tapering off previous treatment [if not already stopped] and initiating the new treatment as indicated by the randomisation arm).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
70 years

Sex
All

Key exclusion criteria
1. Being pregnant or breastfeeding.
2. Subject has failed previously on clozapine due to inefficacy. Treatment duration as ≥4 weeks within an efficacious dose range according to the SmPC.
3. Subject has a known intolerance to clozapine or to all TAU medication options.
4. Meeting any of the contraindications of clozapine or to all TAU medication options, as specified within the applicable SmPC. *
5. Subject has participated in another clinical trial in which the subject received an experimental or investigational drug or agent within 30 days before visit 1.
6. Subject currently uses more than the allowed psychotropic concomitant medication and needs to stay on this medication during the study. **
7. Subject experiences any other significant disease or disorder which, in the opinion of the investigator, may either put the subjects at risk because of participation in the trial, or may influence the result of the trial, or the subject’s ability to participate in the trial.
8. Moderate or high suicidal ideation within the last 2 weeks, defined as a score of 9 or higher on Module B (Suicidality) of the Mini International Neuropsychiatric Interview (MINI v7.0.2) ***
9. Subject meets criteria for current substance use disorder, as confirmed by the Mini International Neuropsychiatric Interview (MINI v7.0.2). Nicotine dependency is allowed, as well as mild alcohol and/or cannabis use disorder (as defined by MINI v7.0.2). Moderate and severe

alcohol and/or cannabis use disorder are not allowed.
10. Subjects who are admitted in the (psychiatric) clinic due to a court or administrative order are not allowed to participate in the study.
11. Subjects who meet the modified Andreasen criteria for remission. ****

* Some SmPCs specify precautions. These are not considered as contraindications (in this trial or in clinical practice). If investigators take precautionary measures, participants can still be initiated on the medication, as this is in line with clinical practice and the SmPC.
** Allowed concomitant medication can be found in Section 8.1 of protocol. For clarity: if the participant is currently on a first-line treatment that is not efficacious and will be switched within the study, this medication does not count for this criterion. This criterion focusses on other, psychotropic concomitant medication (not for the primary diagnosis).
*** The decision to include the participant is at the clinician's discretion. If the score on module B is lower than 9, but the clinician still considers the risk of a suicide attempt too high, it still can be decided to exclude the participant.
****The Andreasen criteria are defined as:
Low scores (≤3) on eight diagnostically relevant symptoms in the Positive and Negative Syndrome Scale (PANSS): P1. Delusions; P3. Hallucinatory behavior; P2. Conceptual disorganization; N1. Blunted affect; N4. Passive/apathetic social withdrawal; N6. Lack of spontaneity and flow of conversation; G5. Mannerisms/posturing; G9. Unusual thought content. Originally, this is coupled with a time criterion (duration of 6 months). The time criterion is not applicable in the study, because it is not feasible as this should have been reported in clinical practice where PANSS is not performed.

Date of first enrolment
31/08/2023

Date of final enrolment
01/12/2026

Locations

Countries of recruitment
United Kingdom

Australia

Austria

Germany

Israel

Italy

Spain

Study participating centre

-
United Kingdom
-

Sponsor information

Organisation
University Medical Center Utrecht

ROR
https://ror.org/0575yy874

Funder(s)

Funder type
Government

Funder Name
Horizon 2020 Framework Programme

Alternative Name(s)
EU Framework Programme for Research and Innovation H2020, Horizon 2020, Horizon 2020 Framework Programme (H2020), Rahmenprogramm Horizont 2020, Horizont 2020, Programa Marco Horizonte 2020, Horizonte 2020, Programme-cadre Horizon 2020, Orizzonte 2020, Programma quadro Orizzonte 2020, H2020

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

This study belongs to a larger consortium that should enable the sharing of data within the consortium within and outside the EU (mandatory). This is explained in the informed consent; subjects consent for this by signing the informed consent. The data will always be managed in

line with GDPR. This is guaranteed via the clinical trial agreement, where this is explained and signed off for or in separate contracts (if needed).

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes