Clinical trial results:
Treating Anxiety to PrevEnt Relapse in Psychosis (TAPERS): a feasibility trial

Summary

EudraCT number	2019-001408-39
Trial protocol	GB
Global end of trial date	31 July 2022

Results information

Result version number	v1 (current)
This version publication date	25 January 2024
First version publication date	25 January 2024
Summary attachment (see zip file)	TAPERS HRA Report (TAPERS END OF PROJECT HRA REPORT.pdf)

Trial information

Trial identification

Sponsor protocol code	SPON1720-19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Eudract: 2019-001408-39

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	30-36 Newport Road, Cardiff, United Kingdom, CF24 0DE
Public contact	Dr Eleri Owen-Jones, Cardiff University, owen-jonesce@cardiff.ac.uk
Scientific contact	Professor Jeremy Hall, Cardiff University, HallJ10@cardiff.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	31 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2022
Global end of trial reached?	Yes
Global end of trial date	31 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the feasibility (including recruitment, retention, adherence, acceptability) of the addition of antidepressant medication to antipsychotic treatment in patients with early psychotic illness to prevent relapse.

Protection of trial subjects:

Participants were adults who had received a diagnosis of psychosis within the last seven years and were being treated by the NHS. All trial participants would continue with their usual care (typically antipsychotic medication).

Participants were followed-up either face-to-face or by telephone (T) at weeks-1(T), -4, -8, -12, -16, -18, -20, -22(T) and -24.

Vital signs (heart rate, blood pressure, respiratory rate, body temperature) were assessed at Baseline, and weeks-4, -18 and -20.

Background therapy:

The question of whether the addition of antidepressant medication to treatment as usual (typically antipsychotic medication) is an effective secondary prevention measure was the focus of this trial.

Evidence for comparator:

N/A, comparator used in this trial was placebo.

Actual start date of recruitment	14 June 2021
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: 4
Worldwide total number of subjects	4
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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was supported by research nurses already employed by 2 Health Boards (C&V and AB) and initially focused on specialist first episode psychosis teams and early intervention services. Trial staff worked with clinical teams to help identify eligible patients from early intervention and community mental health teams within the last 7 years.

Pre-assignment

Screening details:

We maintained detailed screening logs of patients' eligibility and success in recruitment to inform our trial objectives.

Pre-assignment period milestones

Number of subjects started	285[1]
Intermediate milestone: Number of subjects	Excluded: 219
Number of subjects completed	4

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Eligibility not confirmed: 19
Reason: Number of subjects	Eligible but not recruited: 43
Reason: Number of subjects	Excluded at Screening: 219

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The pre-assignment period involved eligibility assessments before participants were enrolled and randomised into the trial. Therefore, more participants entered the pre-assignment period (n = 285) than were enrolled i.e., worldwide number enrolled - n = 4.

Period 1

Period 1 title	Baseline visit
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:

Participants, clinical staff, Chief Investigator, Principal Investigator, research nurses and the trial statisticians remained blinded to treatment allocation throughout the trial. The trial medication allocation was known to key members of the trial team (the study lead, senior trial manager, trial manager and data manager) during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sertraline

Arm description:

50mg/day of IMP (sertraline) for 18 weeks, then 50mg every other day for 4 weeks (weeks 19 to 22), then no IMP in weeks 23 and 24.

Arm type	Experimental
Investigational medicinal product name	Sertraline
Investigational medicinal product code	Active
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment was either a) 50mg/day of IMP (sertraline) for 18 weeks, then 50mg every other day for 4 weeks (weeks 19 to 22), then no IMP in weeks 23 and 24 (a tapered design), or b) placebo to match for an equivalent period.

Arm title	Placebo

Arm description:

Placebo to match

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Active for an equivalent period (daily dose from randomisation till end of week 22).

Number of subjects in period 1	Sertraline	Placebo
Started	2	2
Completed	2	2

Period 2

Period 2 title	Overall Trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Blinding implementation details:

Participants, clinical staff, Chief Investigator, Principal Investigator, research nurses and the trial statisticians remained blinded to treatment allocation throughout the trial. The trial medication allocation was known to key members of the trial team (the study lead, senior trial manager, trial manager and data manager) during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sertraline

Arm description:

50mg/day of IMP (sertraline) for 18 weeks, then 50mg every other day for 4 weeks (weeks 19 to 22), then no IMP in weeks 23 and 24.

Arm type	Experimental

Investigational medicinal product name	Sertraline
Investigational medicinal product code	Active
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment was either a) 50mg/day of IMP (sertraline) for 18 weeks, then 50mg every other day for 4 weeks (weeks 19 to 22), then no IMP in weeks 23 and 24 (a tapered design), or b) placebo to match for an equivalent period.

Arm title	Placebo

Arm description:

Placebo to match

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Active for an equivalent period (daily dose from randomisation till end of week 22).

Number of subjects in period 2	Sertraline	Placebo
Started	2	2
Week 4 follow-up	1	2
Week 8 follow-up	1	2
Week 12 follow-up	1	2
Week 16 follow-up	1	2
Week 18 follow-up	1	2
Week 20 follow-up	1	2
Week 22 follow-up	1	2
Week 24 follow-up	0	1
Completed	0	1
Not completed	2	1
Consent withdrawn by subject	1	-
Physician decision	1	1

Baseline characteristics

Reporting groups

Reporting group title	Baseline visit

Reporting group description: -

Reporting group values	Baseline visit	Total	
Number of subjects	4	4	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	4	4	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	4	4	
Concomitant medication			
All four patients at baseline were using concomitant medication at baseline. One participant in the sertraline arm was using Clozapine and Amisulpride for Schizophrenia, Bisoprolole for hypertension, Itraconozole for fungal infection. Three participants were using Olanzapine, two participants (one in the sertraline arm and one in the placebo arm) were using it for psychosis, whilst the third participant (in the placebo arm) was using Olanzapine, but the disease was missing.			
Units: Subjects			
No concomitant medication	0	0	
Taking concomitant medication	4	4	
Heart rate			
The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: bpm			
arithmetic mean	78.3		
standard deviation	± 14.8	-	
Systolic blood pressure			
The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: mmHg			
arithmetic mean	128.8		
standard deviation	± 9.3	-	
Diastolic blood pressure			

The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: mmHg			
arithmetic mean	72.8		
standard deviation	± 5.4	-	
Respiratory rate			
The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: Breaths/min			
arithmetic mean	12.5		
standard deviation	± 1.0	-	
Body temperature			
The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: C			
arithmetic mean	36.5		
standard deviation	± 0.4	-	

Subject analysis sets

Subject analysis set title	Demographics
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All four patients recruited were single males, three British and one African. Three were living with their parents while one had the living arrangement missing.

Subject analysis set title	Primary Outcome
Subject analysis set type	Intention-to-treat

Subject analysis set description:

To establish the feasibility (including recruitment, retention, adherence, acceptability) of the addition of antidepressant medication to antipsychotic treatment in patients with early psychotic illness to prevent relapse.

Reporting group values	Demographics	Primary Outcome	
Number of subjects	4	4	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	4	4	
From 65-84 years	0	0	
85 years and over	0	0	

Gender categorical Units: Subjects			
Female Male			
Concomitant medication			
All four patients at baseline were using concomitant medication at baseline. One participant in the sertraline arm was using Clozapine and Amisulpride for Schizophrenia, Bisoprolole for hypertension, Itraconozole for fungal infection. Three participants were using Olanzapine, two participants (one in the sertraline arm and one in the placebo arm) were using it for psychosis, whilst the third participant (in the placebo arm) was using Olanzapine, but the disease was missing.			
Units: Subjects			
No concomitant medication	0	0	
Taking concomitant medication	4	4	
Heart rate			
The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: bpm			
arithmetic mean	78.3	78.7	
standard deviation	± 14.8	± 15	
Systolic blood pressure			
The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: mmHg			
arithmetic mean	128.8	133	
standard deviation	± 9.3	± 8.2	
Diastolic blood pressure			
The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: mmHg			
arithmetic mean	72.8	71.7	
standard deviation	± 5.4	± 8.5	
Respiratory rate			
The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: Breaths/min			
arithmetic mean	12.5	12.7	
standard deviation	± 1.0	± 1.2	
Body temperature			
The vital signs measured were Heart rate (BPM), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Respiratory rate (Breaths/min) and Body temperature (C). These were measured to monitor for serotonin syndrome or neuroleptic malignant syndrome and were also measured at weeks 4, 18 and 20. Since no measurement was made at the primary endpoint (week 24), the "primary outcome" value represents the measurement made at the week 20 timepoint.			
Units: C			
arithmetic mean	36.5	36.5	
standard deviation	± 0.4	± 0.4	

End points

End points reporting groups

Reporting group title	Sertraline
Reporting group description:	
50mg/day of IMP (sertraline) for 18 weeks, then 50mg every other day for 4 weeks (weeks 19 to 22), then no IMP in weeks 23 and 24.	
Reporting group title	Placebo
Reporting group description:	
Placebo to match	
Reporting group title	Sertraline
Reporting group description:	
50mg/day of IMP (sertraline) for 18 weeks, then 50mg every other day for 4 weeks (weeks 19 to 22), then no IMP in weeks 23 and 24.	
Reporting group title	Placebo
Reporting group description:	
Placebo to match	
Subject analysis set title	Demographics
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All four patients recruited were single males, three British and one African. Three were living with their parents while one had the living arrangement missing.	
Subject analysis set title	Primary Outcome
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
To establish the feasibility (including recruitment, retention, adherence, acceptability) of the addition of antidepressant medication to antipsychotic treatment in patients with early psychotic illness to prevent relapse.	

Primary: Week 24 Follow-up

End point title	Week 24 Follow-up[1]
End point description:	
Due to the exploratory nature of this feasibility trial no formal statistical hypothesis testing was performed. Primary feasibility outcomes (rates of recruitment, retention, and adherence) overall and per outcome assessment time point (retention and adherence only) are presented as point estimates with 95% exact binomial confidence intervals. These outcomes have been assessed against the 'traffic light system' to guide decisions to progress to definitive evaluations.	
End point type	Primary
End point timeframe:	
24 weeks	

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: The low numbers recruited into this trial did not allow for statistical analysis of the data from 4 participants. Some of the feasibility outcomes were reported using a traffic light system.

End point values	Primary Outcome			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: 1				
Recruitment into the trial	4			
Retention over a 24-week period	3			
Adherence to antidepressant medication	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored from Baseline till follow-up at week-24.

Adverse event reporting additional description:

Adverse Events (AEs) were planned to be collected throughout the trial. This included events deemed to be classed as 'hypomania' or 'mania'. An overdose was not considered an AE and may not have resulted in any noticeable effect on the participant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Sertraline

Reporting group description:

Includes participants randomised to receive Sertraline.

Reporting group title	Placebo

Reporting group description:

This includes all participants randomised to the placebo group.

Serious adverse events	Sertraline	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (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	Sertraline	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	1 / 2 (50.00%)	
Psychiatric disorders			
Mood altered	Additional description: Mood changes for 2 subjects: Week 20: mood changes for both did not meet study withdrawal criteria Week 22: risk to self for 1 of the 2 subject and justified withdrawal After week 22: second subject withdrawn (mental state and mood concerns)		
subjects affected / exposed	1 / 2 (50.00%)	1 / 2 (50.00%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2020	Addressing comments to the MHRA upon their grounds for non-acceptance. These were as follows: i. Tapering the trial design to include a half dose for 4 weeks and no dose for the last 2 weeks; ii. Amend the unblinding process to enable the delegated trial clinician to unblind; iii. Amend wording re: summary of product characteristics (SmPC) in relation to the reference safety information; iv. Addition of details about qualification of research nurses (footnote to inclusion/exclusion criteria amended); v. Addition of two exclusion criteria (inclusion/exclusion criteria); vi. Addition of pregnancy tests and contraception wording (inclusion/exclusion criteria); vii. Renaming a section from Prohibited medication and interaction with other drugs to General Precautions; viii. Addition of Linezolid as a prohibited therapy; ix. Vital signs added to trial schema, and assessments; x. Item 10 of MADRS questionnaire added to the monthly research nurse follow-ups; xi. End of trial wording amended; xii. Treatment prescribing and dispensing amended to simplify the process.
13 January 2021	The Information Sheet for Family Member / Partner interviews (this was not submitted with initial approval paperwork).
10 May 2021	Adjustment to the timing of the secondary outcomes to bring them in line with the end of the main IMP treatment period, including updating the Participant Information Sheet; update to the Reference Safety Information; and the option of posting IMP to trial participants due to the covid-19 pandemic.
26 July 2021	Change to first eligibility criteria from three to seven years. Clarification to source data being used.

Notes:

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.

High ineligibility (many already on SSRIs); very demanding trial regime (staff resourcing & assessments) maximise inclusion with more pragmatic design in future; Covid-19 negatively impacted the trial; treatment misallocation – no sertraline received

Notes: