Clinical trial results:
Research into Antipsychotic Discontinuation and Reduction (RADAR): A Randomised Controlled Trial

Summary

EudraCT number	2016-000709-36
Trial protocol	GB
Global end of trial date	10 March 2022

Results information

Result version number	v1 (current)
This version publication date	29 March 2024
First version publication date	29 March 2024
Summary attachment (see zip file)	Final Paper Published in the Lancet Psychiatry 2023 (Radar final paper_1023.pdf)

Trial information

Trial identification

Sponsor protocol code	15/0947

Additional study identifiers

ISRCTN number	ISRCTN90298520
ClinicalTrials.gov id (NCT number)	NCT03559426
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Priment Clinical Trials Unit staff, Priment Clinical Trials Unit University College London, 44 020 7679 2000, priment@ucl.ac.uk
Scientific contact	Priment Clinical Trials Unit staff, Priment Clinical Trials Unit University College London, 44 020 7679 2000, priment@ucl.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	18 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the benefits and risks of a supported programme of antipsychotic dose reduction, and where feasible discontinuation, in adults with multiple episode schizophrenia and psychotic disorders. These benefits and risks will be established in comparison to a control group from the same clinical population who will maintain their current antipsychotic regimen.

The hypothesised principal outcome of the trial is that the programme of reduction will improve the social functioning of participants without increasing the risk of having a severe relapse.

The principal secondary outcome will be severe relapse. Other secondary outcomes include quality of life, neuropsychological function, side effects and employment rates.

Protection of trial subjects:

The eligibility criteria were designed to exclude people with known high risks of causing harm to themselves or
other people. In addition, the gradual nature of the antipsychotic reduction enabled detection and treatment
of early signs of relapse. All participants received usual care and monitoring of their mental state and behaviour by their clinical team. Those randomised to antipsychotic reduction had increased contact with a psychiatrist
for the duration of the reduction, mirroring usual clinical practice of someone undergoing a significant reduction of medication.

A Data Safety and Monitoring Board (DSMB) and Programme Steering Committee provided independent oversight of the trial. The DSMB safeguarded the interests of trial participants by assessing the safety and efficacy of the interventions during the trial, and monitoring its conduct and it made recommendations to the steering committee. There was no formal interim analysis, but the DSMB continually reviewed all adverse events
data, with the agreement that the trial would be stopped if it was judged that there was a substantial increase in serious adverse events that are likely to be related to the intervention.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 January 2017
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: 253
Worldwide total number of subjects	253
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)	238
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants meeting the eligibility criteria were recruited from a variety of clinical teams in mental health services in the UK. Potential participants were identified initially by clinical staff or recruited by advertisements placed in clinical settings. If agreed, participants were sent details of the study and a baseline assessment arranged.

Pre-assignment

Screening details:

4157 people were screened by the clinical teams to ensure they met the strict eligibility criteria, including capacity. After receiving informed consent to participate, participants were randomised to maintenance treatment or the antipsychotic reduction arm. This was an open, parallel group randomised trial with concealed, individual randomisation.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Assessor, Data analyst[2]

Blinding implementation details:

Each participant and their clinicians were aware of the treatment allocation, but the researchers who conducted assessments were masked to allocation as far as possible and analysis was also conducted masked to group identity. Researchers were instructed to record incidences when they suspected they might have been unmasked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Reduction

Arm description:

An antipsychotic reduction strategy supported by the participant’s treating clinician, with an individualised reduction schedule provided as a guide.

Arm type	Experimental
Investigational medicinal product name	N/A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

Not applicable for this trial.

Arm title	Maintenance

Arm description:

Participants received maintenance antipsychotic treatment.

Arm type	Active comparator
Investigational medicinal product name	N/A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

Not applicable for this trial.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: Participants and treating clinicians were not blinded because participants started on different antipsychotic regimes, and those within the intervention group followed an individualised reduction protocol.
Members of the research team conducting outcome assessments were blinded to treatment allocation.

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Participants and treating clinicians were not blinded because participants started on different antipsychotic regimes, and those within the intervention group followed an individualised reduction protocol.
Members of the research team conducting outcome assessments were blinded to treatment allocation.

Number of subjects in period 1	Reduction	Maintenance
Started	126	127
6 month assessment	106	116
12 month assessment	95	98
24 month assessment	91	99
Completed	91	99
Not completed	35	28
Consent/contact withdrawn, death, hospitalisation	35	28

Baseline characteristics

Reporting groups	
Reporting group title	Reduction
Reporting group description:	
An antipsychotic reduction strategy supported by the participant's treating clinician, with an individualised reduction schedule provided as a guide.	
Reporting group title	Maintenance
Reporting group description:	
Participants received maintenance antipsychotic treatment.	

Reporting group values	Reduction	Maintenance	Total
Number of subjects	126	127	253
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	117	121	238
From 65-84 years	9	6	15
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	46.6	46.0	
standard deviation	± 12.2	± 11.5	-
Gender categorical Units: Subjects			
Female	40	42	82
Male	85	83	168
Transgender	1	2	3
Ethnicity Units: Subjects			
White	89	82	171
Black	25	27	52
Asian	8	8	16
Other	4	8	12
Not recorded	0	2	2
Diagnosis Units: Subjects			
Schizophrenia	87	87	174
Other Psychotic Disorder	39	40	79
Marital Status Units: Subjects			
Single, separated, divorced or widowed	106	110	216

Married, cohabiting or in a partnership	20	17	37
First Language Units: Subjects			
English	106	114	220
Other	20	13	33
Highest educational achievement Units: Subjects			
Primary and secondary education to age 16 years	49	36	85
Primary and secondary education to age 18 years	22	27	49
Tertiary or further education	40	56	96
Other general education	14	7	21
Not recorded	1	1	2
Employment Units: Subjects			
Employed, voluntary work or in education	38	36	74
Not working or in education	88	89	177
Not recorded	0	2	2
Length of time in contact with mental health services Units: Subjects			
0-3 years	11	6	17
4-10 years	34	28	62
11-15 years	20	23	43
16-20 years	20	22	42
>20 years	41	48	89
Age when first referred to mental health services Units: Subjects			
<20 years	26	27	53
20-30 years	57	67	124
31-40 years	25	22	47
≥41 years	18	11	29
Alcohol use in the past month Units: Subjects			
Once a month or less	80	82	162
Two to four times a month	24	20	44
Two or more times a week	22	19	41
Not recorded	0	6	6
Recreational drugs used in the past month Units: Subjects			
Recreational drugs used	11	14	25
None	115	113	228
Years of completed education Units: Years			
arithmetic mean	14	14	
standard deviation	± 3.3	± 3.9	-
Antipsychotic medication dose in chlorpromazine equivalents, mg Units: Milligrams			

median	300	300	
full range (min-max)	200 to 450	200 to 400	-
Number of previous mental health admissions Units: Number of admissions			
median	3	3	
full range (min-max)	1 to 5	1 to 5	-

End points

End points reporting groups

Reporting group title	Reduction
Reporting group description:	
An antipsychotic reduction strategy supported by the participant’s treating clinician, with an individualised reduction schedule provided as a guide.	
Reporting group title	Maintenance
Reporting group description:	
Participants received maintenance antipsychotic treatment.	

Primary: Social Functioning Scale (SFS) score

End point title	Social Functioning Scale (SFS) score
End point description:	
Scale used to assess social engagement/withdrawal, interpersonal communication, independence performance, recreational activities, prosocial, independence - competence and occupation and employment. The scale uses the mean of the standardised scores from each domain.	
End point type	Primary
End point timeframe:	
Social Functioning Score was measured at 24 months post baseline.	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	94		
Units: Overall score				
arithmetic mean (standard deviation)				
SFS score	105.7 (± 10.5)	106.7 (± 9.7)		

Statistical analyses

Statistical analysis title	Social Functioning Scale score
Statistical analysis description:	
With robust standard errors.	
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.859
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	2.33

Secondary: Severe relapse

End point title	Severe relapse

End point description:

Rates of severe relapse defined as hospitalisation in a mental health inpatient unit.

Less severe cases of relapse, not requiring admission to hospital, were also assessed by a blinded 'endpoint committee' based on summary information prepared from clinical records according to predefined criteria.

End point type	Secondary

End point timeframe:

Till the end of the follow-up.

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	127		
Units: Hospitalisations				
Hospitalisations	34	17		

Attachments (see zip file)	Kaplan Meier plot for severe relapse/Screenshot 2023-11-26 at

Statistical analyses

Statistical analysis title	Time to severe relapse

Statistical analysis description:

Time to severe relapse was analysed with survival analysis using a Cox proportional hazards model with robust SEs. The extent to which there was a departure from constant proportional hazards was assessed statistically using Schoenfeld residuals. Logistic models with robust SEs on the occurrence of severe relapse within 24 months and the combination of severe and less severe relapse were conducted as supportive analyses.

Comparison groups	Maintenance v Reduction
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007 [1]
Method	Cox Proportional Hazard regression
Parameter estimate	Hazard ratio (HR)
Point estimate	2.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	3.99

Notes:

[1] - No evidence that the assumption of proportional hazards was violated using Schoenfeld residuals (p=0.59).

Statistical analysis title	Severe relapse at any time to the end of the trial
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	4.56

Secondary: Severe relapse at any time during 24 months

End point title	Severe relapse at any time during 24 months

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	127		
Units: Admissions	32	17		

Statistical analyses

Statistical analysis title	Severe relapse at any time during 24 months
Comparison groups	Reduction v Maintenance

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	4.22

Secondary: Non-severe relapse at any time during 24 months

End point title	Non-severe relapse at any time during 24 months
End point description:	

End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	127		
Units: Relapse				
24 months	20	11		

Statistical analyses

Statistical analysis title	Non-severe relapse at any time during 24 months
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	4.35

Secondary: Any relapse at any time during 24 months

End point title	Any relapse at any time during 24 months

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	127		
Units: Relapse				
Any relapse	52	28		

Statistical analyses

Statistical analysis title	Any relapse at any time during 24 months
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	4.3

Secondary: Psychiatric bed days during 24 months

End point title	Psychiatric bed days during 24 months

End point description:

There was no difference in the median psychiatric bed days between groups. Mean bed days were higher for those in the reduction group, but the data were highly skewed.

End point type	Secondary

End point timeframe:

24 months

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	121		
Units: Number of bed days	0	0		

Statistical analyses

Statistical analysis title	Number of psychiatric bed days during 24 months

Statistical analysis description:

Incidence rate ratio

The interquartile range (IQR) for the reduction group was 0, 31, and IQR for the maintenance group was 0, 0

Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	other[2]
Method	Zero inflated neg- binomial regression
Parameter estimate	Incidence rate ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.7

Notes:

[2] - Number of inpatient days was analysed using Poisson mixed models, with number by 24 months as the response variable, and the log(e) of the number of days of follow up as an offset. A random effect for Trust was included.
Method used was zero inflated negative binomial regression with robust SEs.

Secondary: PANSS positive symptoms subscale

End point title	PANSS positive symptoms subscale

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	91		
Units: Scale				
median (full range (min-max))	10 (8 to 14)	10 (8 to 14)		

Statistical analyses

Statistical analysis title	PANSS positive symptoms sub scale score
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	1.56

Secondary: PANSS negative symptoms sub scale	
End point title	PANSS negative symptoms sub scale
End point description:	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	88		
Units: Scale				
median (full range (min-max))	9 (8 to 13)	10 (8 to 14)		

Statistical analyses

Statistical analysis title	PANSS negative symptoms sub scale
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	0.32

Secondary: Positive and Negative Syndrome Scale (PANSS) total score

End point title	Positive and Negative Syndrome Scale (PANSS) total score
End point description:	

End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	59		
Units: Scale score				
median (full range (min-max))	43 (36 to 54)	48 (38 to 63)		

Statistical analyses

Statistical analysis title	PANSS total score
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.18
upper limit	1.97

Secondary: Manchester Short Assessment of Quality of Life (MANSA)

End point title	Manchester Short Assessment of Quality of Life (MANSA)
End point description:	

A measure of subjective quality of life.

12 questions on participants' satisfaction with various aspects of their life. The scale is a mean of each item assessing participants' satisfaction with various aspects of their life.

End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	89		
Units: Scale score				
arithmetic mean (standard deviation)	4.6 (± 1.0)	4.7 (± 0.7)		

Statistical analyses

Statistical analysis title	MANSA
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.14

Secondary: Objective Social Outcomes Index (SIX)

End point title	Objective Social Outcomes Index (SIX)
End point description:	

End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	90		
Units: Scale score				
arithmetic mean (standard deviation)	3.3 (± 1.2)	3.3 (± 1.1)		

Statistical analyses

Statistical analysis title	SIX
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.26

Secondary: Glasgow Antipsychotic Side-effect Scale (GASS)

End point title	Glasgow Antipsychotic Side-effect Scale (GASS)

End point description:

A 22 item scale with 20 questions using a Likert type response from 0=never to 3=every day. Eleven questions have been added to the scale from other side effect questionnaires, making it a modified version, with a total score of 99.

End point type	Secondary

End point timeframe:

24 months

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	68		
Units: Scale score				
arithmetic mean (standard deviation)	21.9 (± 15.5)	25.3 (± 16.0)		

Statistical analyses

Statistical analysis title	GASS
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-3.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.77
upper limit	0.81

Secondary: Client Satisfaction Questionnaire (CSQ)	
End point title	Client Satisfaction Questionnaire (CSQ)
End point description:	
An 8 item measure which each item is scored on a four point Likert scale from 1 (lowest degree of satisfaction) to 4 (highest degree of satisfaction), giving an overall score between 8 and 32.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	84		
Units: Scale score				
median (full range (min-max))	25 (19 to 28)	25 (22 to 29)		

Statistical analyses

Statistical analysis title	CSQ-8
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.46
upper limit	0.85

Secondary: Medication Adherence Report Scale (MARS-5)

End point title	Medication Adherence Report Scale (MARS-5)

End point description:

Antipsychotic medication adherence. A five item measure which is scored on a five point Likert scale with 1=always and 5=never.

Item scores are summed to give an overall score between 5 and 25.

End point type	Secondary

End point timeframe:

24 months

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	85		
Units: Scale score				
median (full range (min-max))	25 (23 to 25)	25 (23 to 25)		

Statistical analyses

Statistical analysis title	MARS-5
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	1.21

Secondary: Questionnaire of the Process of Recovery (QPR)

End point title	Questionnaire of the Process of Recovery (QPR)

End point description:

22 item scaled with Likert scale responses. Total measure ranged between 0-88, with higher scores indicating a more positive outlook and being further along the recovery process.

End point type	Secondary

End point timeframe:

24 months

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: Scale score				
arithmetic mean (standard deviation)	41.5 (± 9.5)	41.1 (± 9.5)		

Statistical analyses

Statistical analysis title	QPR-15
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.39
upper limit	2.32

Secondary: Arizona Sexual Experience Scale (ASEX)

End point title	Arizona Sexual Experience Scale (ASEX)

End point description:

Consists of five items, scored on a six point Likert scale.

Includes a sex specific question; people were encouraged to complete the question most suited to their gender identity.

End point type	Secondary

End point timeframe:

24 months

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: Scale score				
arithmetic mean (standard deviation)	14.6 (± 4.2)	17.4 (± 6.7)		

Statistical analyses

Statistical analysis title	ASEX
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.06
upper limit	3.02

Secondary: Bodyweight	
End point title	Bodyweight
End point description: Measured in kilograms	
End point type	Secondary
End point timeframe: 24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	71		
Units: Kilograms				
arithmetic mean (standard deviation)	89.6 (± 25)	85.5 (± 18.4)		

Statistical analyses

Statistical analysis title	Bodyweight
Comparison groups	Reduction v Maintenance

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.29
upper limit	7.83

Secondary: Cognitive tests – Digit span

End point title	Cognitive tests – Digit span
End point description:	
The overall score is the sum of the forward and backward trials.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	88		
Units: Score				
arithmetic mean (standard deviation)	14.7 (± 4.9)	15.4 (± 4.7)		

Statistical analyses

Statistical analysis title	Digit span
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	0.34

Secondary: Cognitive tests - Digit symbol substitution

End point title	Cognitive tests - Digit symbol substitution
End point description:	
Scored one point for each correctly drawn symbol in the time limit	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	66		
Units: Score				
arithmetic mean (standard deviation)	47.2 (± 20.8)	47.7 (± 20.9)		

Statistical analyses

Statistical analysis title	Digit symbol substitution
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	2.33

Secondary: Cognitive tests - Auditory Verbal Learning Task

End point title	Cognitive tests - Auditory Verbal Learning Task
End point description:	
Scored by the number of words correctly remembered in each trial. The scores from the trials are added to give an overall score.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	85		
Units: Number of words correctly recalled				
arithmetic mean (standard deviation)	37.0 (± 16.1)	38.2 (± 12.6)		

Statistical analyses

Statistical analysis title	Auditory verbal learning task
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.37
upper limit	2.55

Secondary: Cognitive tests - Trail making

End point title	Cognitive tests - Trail making
End point description:	

End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	69		
Units: Minutes				
median (full range (min-max))	48 (35 to 61)	44 (34 to 67)		

Statistical analyses

Statistical analysis title	Trail making
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.71
upper limit	10.49

Secondary: Cognitive tests - Verbal Fluency	
End point title	Cognitive tests - Verbal Fluency
End point description: Scored by the total number of each correct animal, minus number of errors.	
End point type	Secondary
End point timeframe: 24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	83		
Units: Total number of words (minus errors)				
arithmetic mean (standard deviation)	17.4 (± 6.8)	17.3 (± 5.5)		

Statistical analyses

Statistical analysis title	Verbal fluency
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	1.6

Secondary: Employment status	
End point title	Employment status
End point description:	
Employment status was assessed using the employment sub scale of the SFS	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Reduction	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	99		
Units: Employment status				
Employed, voluntary work or in education	18	20		
Not working or in education	73	79		

Statistical analyses

Statistical analysis title	Employment status
Statistical analysis description:	
Employment status was analysed using logistic regression with robust SEs.	
Comparison groups	Reduction v Maintenance
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reviews were held at:
- Baseline
- Pilot trial 3m data collection
- 6 month follow up
- 12 month follow up
- 24 month follow up

Adverse event reporting additional description:

Serious adverse events were more common in the reduction group, largely due to a higher number of hospital admissions for relapse. Non-serious adverse events were more common in the reduction group, but the number of people experiencing one was lower in the reduction than the maintenance group.

Assessment type	Systematic

Dictionary used

Dictionary name	n/a
Dictionary version	n/a

Reporting groups

Reporting group title	Reduction group

Reporting group description:

Antipsychotic reduction arm

Reporting group title	Maintenance group

Reporting group description:

Antipsychotic maintenance treatment group

Serious adverse events	Reduction group	Maintenance group	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 126 (38.89%)	29 / 127 (22.83%)	
number of deaths (all causes)	8	4	
number of deaths resulting from adverse events			
Investigations			
Psychiatric care	Additional description: Serious adverse events included death, hospital admissions, life threatening events and others. Please note that causality was assessed according to the antipsychotic participants were taking, not the randomised intervention.		
subjects affected / exposed	49 / 126 (38.89%)	29 / 127 (22.83%)	
occurrences causally related to treatment / all	12 / 93	11 / 64	
deaths causally related to treatment / all	0 / 8	1 / 4	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Reduction group	Maintenance group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 126 (69.84%)	97 / 127 (76.38%)	
Investigations			
Psychiatric care			
subjects affected / exposed	88 / 126 (69.84%)	97 / 127 (76.38%)	
occurrences (all)	691	476	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2017	Change of primary outcome measure, from the Groningen Social Disabilities Scale to the Social Functioning scale. Protocol: Update to one inclusion/exclusion criteria that was listed incorrectly. Recruitment and patient identification amended in order to recruit through service user groups and networks. Reporting of SAEs and pregnancies made clearer. Reference safety information amended to make it clearer how to determine expectedness. The 'questionnaire about the process of recovery (QPR)' added as it was omitted in error. Primary outcome measure amended and power calculation subsequently amended. Guidance for psychiatrists regarding how to manage increased symptoms and relapse updated.
30 October 2017	(REC only) Protocol: Social Cognition Questionnaire added to Secondary Outcomes. Exclusion criteria updated to clarify that patients subject to section 37/41 of the Mental Health Act are not eligible. Clarification added that data will be collected from medical records throughout the course of the study.
30 April 2018	Protocol: Safety reporting procedures amended to restrict the types of events that need to be reported. New list of Investigational Medicinal Products listed in appendix. RSI for assessment of expectedness amended.
08 March 2019	(REC only) Protocol: Addition of information relating to conducting qualitative interviews.
20 May 2019	(REC only) Protocol: Recruitment extended to 31 January 2020. Updated to include all established antipsychotic drugs that are used in Europe/USA; Melperone added. Social Outcomes Index added to secondary outcomes.
28 June 2019	Protocol: Updated to remove that antipsychotic drugs used in the USA can be used (added in error).
20 April 2020	Protocol and PIS: Updated to allow for follow up assessments to be conducted remotely, in response to the COVID-19 pandemic.
14 July 2020	Protocol: Updated to include interviews with participants from the maintenance group in the qualitative sub-study.

20 May 2021	Protocol: Update to qualitative interviews. Updates to IMP SmPC appendix.

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.

Recruitment was challenging and some participants did not adhere to their randomised treatment programme.
The Covid pandemic affected the social functioning measure.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37778356