Clinical trial results:
A multi-centre, double-blind, individually randomised, placebo-controlled, parallel arm RCT with 12-week follow-up to establish the clinical and cost effectiveness of amisulpride augmentation of clozapine in treatment-resistant schizophrenia unresponsive to clozapine

Summary

EudraCT number	2010-018963-40
Trial protocol	GB
Global end of trial date	25 March 2015

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	08 April 2016

Trial information

Trial identification

Sponsor protocol code	CRO1498

Additional study identifiers

ISRCTN number	ISRCTN68824876
ClinicalTrials.gov id (NCT number)	NCT01246232
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Exhibition Road, London, United Kingdom, SW7 2AZ
Public contact	Clinical Trials Office, Centre for Mental Health, Imperial College London, v.leeson@imperial.ac.uk
Scientific contact	Clinical Trials Office, Centre for Mental Health, Imperial College London, v.leeson@imperial.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2015
Global end of trial reached?	Yes
Global end of trial date	25 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test carefuly the possible benefits and problems when the antipsychotic amisulpride or a dummy tablet ('placebo') is added to clozapine for 12 weeks in people whose schizophrenia illness has not been helped much by any antipsychotic medication on its own, and who are now taking clozapine, but again with not much improvement.

Protection of trial subjects:

Thorough monitoring of adverse events and participant wellbeing occurred as part of the assessment process. During assessment and testing, breaks were provided to minimise possible fatigue or stress, and if indicated,the assessments were spread over several days.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2011
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: 68
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	68
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

•Treatment for at least 12 weeks at a stable dose of 400mg or more of clozapine a day, unless the size of the dose was limited by side effects
•A total score of 80+ on the Positive and Negative Syndrome Scale (PANSS)
•A Clinical Global Impressions (CGI) score of 4+
•A Social and Occupational Functioning Assessment Scale (SOFAS) score of <41

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Clozapine + Amisulpride

Arm description: -

Arm type	Experimental
Investigational medicinal product name	amisulpride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 400mg amisulpride or one matching placebo capsule for the first 4 weeks, after which there was a clinical option to titrate the dosage of amisulpride up to 800mg or two matching placebo capsules for the remaining 8 weeks.

Arm title	Clozapine + placebo

Arm description: -

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

Dosage and administration details:

Participants received 400mg amisulpride or one matching placebo capsule for the first 4 weeks, after which there was a clinical option to titrate the dosage of amisulpride up to 800mg or two matching placebo capsules for the remaining 8 weeks.

Number of subjects in period 1	Clozapine + Amisulpride	Clozapine + placebo
Started	35	33
Six Weeks	32	26
Completed	32	21
Not completed	3	12
Consent withdrawn by subject	2	3
IMP discontinued	-	5
Protocol deviation	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Clozapine + Amisulpride
Reporting group description: -	
Reporting group title	Clozapine + placebo
Reporting group description: -	

Reporting group values	Clozapine + Amisulpride	Clozapine + placebo	Total
Number of subjects	35	33	68
Age categorical Units: Subjects			
Adults (18-64 years)	35	33	68
Age continuous Units: years			
arithmetic mean	39	40	
standard deviation	± 11	± 10	-
Gender categorical Units: Subjects			
Female	11	10	21
Male	24	23	47

Subject analysis sets	
Subject analysis set title	Baseline data analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description: All data present are analysed.	
Subject analysis set title	Endpoint
Subject analysis set type	Intention-to-treat
Subject analysis set description: Includes all people who have data at this time point	

Reporting group values	Baseline data analysis	Endpoint	
Number of subjects	68	57	
Age categorical Units: Subjects			
Adults (18-64 years)	68		
Age continuous Units: years			
arithmetic mean	39		
standard deviation	± 10	±	
Gender categorical Units: Subjects			
Female	21		
Male	47		

End points

End points reporting groups

Reporting group title	Clozapine + Amisulpride
Reporting group description: -	
Reporting group title	Clozapine + placebo
Reporting group description: -	
Subject analysis set title	Baseline data analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All data present are analysed.	
Subject analysis set title	Endpoint
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all people who have data at this time point	

Primary: 20% reduction in total PANSS score from baseline

End point title	20% reduction in total PANSS score from baseline
End point description:	
End point type	Primary
End point timeframe:	
12 weeks after baseline	

End point values	Clozapine + Amisulpride	Clozapine + placebo	Endpoint	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	25	57[1]	
Units: percentage				
Less than 20% reduction in PANSS from baseline	18	15	33	
20% or more reduction in PANSS from baseline	14	10	24	

Notes:

[1] - All those with data were analysed.

Statistical analyses

Statistical analysis title	Primary outcome statistical analysis

Statistical analysis description:

The primary outcome was analysed using logistic regression, adjusting for baseline PANSS score. Results are presented in terms of the intervention (Clozapine + Amisulpride) arm.

Comparison groups	Clozapine + Amisulpride v Clozapine + placebo

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.42

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 Nov 2011 - 24 Jun 2015

Adverse event reporting additional description:

The Antipsychotic Non-Neurological Side-Effects Rating Scale was carried out at each timepoint.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	amisulpride

Reporting group description: -

Reporting group title	placebo

Reporting group description: -

Serious adverse events	amisulpride	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 34 (2.94%)	2 / 29 (6.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Psychotic behaviour	Additional description: worsening of psychotic symptoms requiring hospitalisation		
subjects affected / exposed	0 / 34 (0.00%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	amisulpride	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 34 (61.76%)	10 / 29 (34.48%)	

Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) Heart rate irregular subjects affected / exposed occurrences (all)	 2 / 34 (5.88%) 4 2 / 34 (5.88%) 3	 0 / 29 (0.00%) 0 1 / 29 (3.45%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	 6 / 34 (17.65%) 12	 2 / 29 (6.90%) 2	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	 3 / 34 (8.82%) 3	 1 / 29 (3.45%) 1	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 6 / 34 (17.65%) 12	 1 / 29 (3.45%) 1	
Endocrine disorders Hyperprolactinaemia subjects affected / exposed occurrences (all)	 11 / 34 (32.35%) 11	 0 / 29 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2013	- A change to the way in which participants are un-blinded at the end. Rather than the participant being able to request the information at the end of their participation, they will be advised in the Patient information Sheet that they will be send this information at the end of their participation, and a copy of this notification also sent directly to the referring psychiatrist. - The addition of an option for the prescriber to provide a further 28-day supply of study medication after the final 12-week follow-up assessment. In combination with the direct un-blinding of the referring psychiatrist, this will allow time for participants allocated to the active (amisulpride) arm of the trial to be provided with a standard prescription of amisulpride, and therefore allow an uninterrupted supply of medication where the participant and prescribing clinician agree that this is desirable. - The introduction of a small remuneration to participants in recognition of any expenses incurred (e.g. travel) and inconvenience. This will be £20 for the screening and baseline assessment, £20 for the 6-week assessment, and £20 for the 12-week assessment. Where a participant chooses to discontinue study medication but not to withdraw from the study, this payment will still be made for the completion of assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported