Clinical trial results:
A pilot study of Aripiprazole treatment for antipsychotic induced hyperprolactinaemia in young patients with severe mental illness and learning disabilities.

Summary

EudraCT number	2009-011228-73
Trial protocol	GB
Global end of trial date	31 December 2014

Results information

Result version number	v1 (current)
This version publication date	21 September 2016
First version publication date	21 September 2016
Summary attachment (see zip file)	Aripiprazole and Prolactin Study (Aripiprazole and Prolactin Study.docx)

Trial information

Trial identification

Sponsor protocol code	OCTUMI-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01085383
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Clinical Trials and Research Governance, Block 60, Churchill Hospital, Old Road, Oxford, United Kingdom, OX3 7LE
Public contact	Dr Valeria Frighi, Dr. Valeria Frighi University of Oxford, 44 1865223779, valeria.frighi@psych.ox.ac.uk
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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	03 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2014
Global end of trial reached?	Yes
Global end of trial date	31 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Can addition of aripiprazole to current antipsychotic normalize or reduce prolactin sufficiently to restore normal function of the ovaries and the testes?

Protection of trial subjects:

Trial procedures were minimal, namely measuring of height and weight, and blood sampling. Trial subjects were asked during the visit at which stage they would like to have their physical measurements and the blood sample taken, and their wishes were followed. Additionally, for participants with a learning disability, a trusted carer was always present, so that any potential distress was minimised.

Background therapy:

There were no treatments that were not tests or comparator products which were used across all groups in the trial.

Evidence for comparator:

All patients in the trial were using an antipsychotic medication causing hyperprolactinaemia. These antipsychotics were risperidone, paliperidone, amisulpride and sulpiride. However, it became apparent during the trial and on review of the literature, that the response to the test drug aripiprazole, was different according to whether participants were taking risperidone or paliperidone or were taking amisulpride or sulpiride. Because of this, analyses were carried out by comparing the two groups of patients.

Actual start date of recruitment	27 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	2
Adults (18-64 years)	13
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place between September 2010 and June 2014. It was very prolonged due to the unexpected paucity of referrals of patients with known or suspected antipsychotic-induced hyperprolacytinaemia by local psychiatrists and General Practitioners, and to a high exclusion rate. 15 patients were recruited.

Pre-assignment

Screening details:

70 patients were referred to the study. 55 of these were excluded due to patient's refusal (8) or legal representative's refusal (1), normal prolactin (11), regular periods (7), menopause (3), use of sex hormones treatment (4), normal testosterone (14), primary gonadal failure (5), uncontrolled diabetes (2).

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was not blinded.

Arms

Arm title	Aripiprazole

Arm description:

There is only one arm as this is an uncontrolled intervention study (each participant serves as their own controls as changes are measured according to dose of drug received).

Arm type	single arm
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	
Other name	Abilify
Pharmaceutical forms	Buccal tablet, Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Aripiprazole was administered at a dose of 1.5 to 10 mg daily according to prolactin response. It was taken by participants as a tablet or oral solution in a once daily administration in the morning, after food.

Number of subjects in period 1	Aripiprazole
Started	15
Completed	12
Not completed	3
Physician decision	1
Consent withdrawn by subject	2

Baseline characteristics

Reporting groups

Reporting group title	Baseline period

Reporting group description: -

Reporting group values	Baseline period	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age was 16 years and above			
Units: years			
median	39		
full range (min-max)	16 to 56	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	8	8	
Type of antipsychotic			
Type of antipsychotic with which trial subjects were treated by their clinicians			
Units: Subjects			
Risperidone or paliperidone	9	9	
Amisulpride or sulpiride	6	6	
Prolactin			
Blood sample collected in the morning before food			
Units: mU/L			
median			
full range (min-max)		-	

Subject analysis sets

Subject analysis set title	Subjects completing trial (baseline prolactin values)
Subject analysis set type	Per protocol

Subject analysis set description:

These are the subjects who completed the trial, namely those who reached a stable dose of aripiprazole and in whom therefore efficacy analysis could be done, when their prolactin was measured before starting aripiprazole.

Subject analysis set title	Subjects completing trial (prolactin values on aripiprazole)
Subject analysis set type	Per protocol

Subject analysis set description:

These are the subjects who completed the trial, namely those who reached a stable dose of aripiprazole and in whom therefore efficacy analysis could be done, when their prolactin was measured during follow-up at a stable aripiprazole dose.

Reporting group values	Subjects completing trial (baseline prolactin values)	Subjects completing trial (prolactin values on aripiprazole)	
Number of subjects	12	12	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age was 16 years and above			
Units: years median full range (min-max)	 36.5 16 to 56		
Gender categorical Units: Subjects			
Female Male	6 6		
Type of antipsychotic			
Type of antipsychotic with which trial subjects were treated by their clinicians			
Units: Subjects			
Risperidone or paliperidone Amisulpride or sulpiride	8 4		
Prolactin			
Blood sample collected in the morning before food			
Units: mU/L median full range (min-max)	 942.5 480 to 3113		

End points

End points reporting groups

Reporting group title	Aripiprazole

Reporting group description:

There is only one arm as this is an uncontrolled intervention study (each participant serves as their own controls as changes are measured according to dose of drug received).

Subject analysis set title	Subjects completing trial (baseline prolactin values)
Subject analysis set type	Per protocol

Subject analysis set description:

These are the subjects who completed the trial, namely those who reached a stable dose of aripiprazole and in whom therefore efficacy analysis could be done, when their prolactin was measured before starting aripiprazole.

Subject analysis set title	Subjects completing trial (prolactin values on aripiprazole)
Subject analysis set type	Per protocol

Subject analysis set description:

These are the subjects who completed the trial, namely those who reached a stable dose of aripiprazole and in whom therefore efficacy analysis could be done, when their prolactin was measured during follow-up at a stable aripiprazole dose.

Primary: Decrease in Prolactin

End point title	Decrease in Prolactin

End point description:

End point type	Primary

End point timeframe:

Decrease in Prolactin between baseline and following aripiprazole up-titration

End point values	Subjects completing trial (baseline prolactin values)	Subjects completing trial (prolactin values on aripiprazole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: mU/L				
median (full range (min-max))	942.5 (480 to 3113)	565.5 (251 to 3015)		

Statistical analyses

Statistical analysis title	Related samples Mann-Whitney U test

Statistical analysis description:

Prolactin levels at baseline were compared with prolactin levels achieved following up-titration of aripiprazole

Comparison groups	Subjects completing trial (baseline prolactin values) v Subjects completing trial (prolactin values on aripiprazole)

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Duration of the trial

Adverse event reporting additional description:

Information about aripiprazole related adverse events and Serious Adverse Events (whether or not study drug related) was collected at each study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	2016

Reporting groups

Reporting group title	Aripiprazole

Reporting group description:

There is only one arm as this is an uncontrolled intervention study (each participant serves as their own controls as changes are measured according to dose of drug received).

Serious adverse events	Aripiprazole		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Depression	Additional description: The patient was hospitalised for severe depression. This was unrelated to the study drug, which was continued.		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.01 %

Non-serious adverse events	Aripiprazole		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
Cardiac disorders			
Tachycardia	Additional description: The patient developed bouts of tachycardia, unaccompanied by any other symptoms, at a dose of aripiprazole of 7.5 mg daily. The tachycardia disappeared on stopping the study drug.		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye disorders			

Hazy vision	Additional description: One subject reported hazy vision at an aripiprazole dose of 10 mg. Vision returned normal on decreasing aripiprazole to 7.5 mg		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Psychiatric disorders			
Irritability	Additional description: The patient developed irritability and worsening of insomnia at an aripiprazole dose of 7.5 mg. This subsided on stopping the drug.		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2012	The age range was amended from 16 to 25 years originally to 16 years and above. Subjects lacking capacity for informed consent were included. The starting dose of aripiprazole was reduced to 2.5 mg and the up-titration schedule modified to 2.5 mg step increases. We specified that the study was open to patients with learning disabilities and patients with any type of severe mental illness, rather than only schizophrenia, requiring long-term antipsychotic treatment. The rationale of some of these changes was to increase the number of patients recruited, to make the study more relevant to patients with a learning disability as many of them lack capacity to consent, and to include any patients on chronic antipsychotic therapy. The changes in dose were due to the publication of a study showing efficacy of low dose aripiprazole and to the clinical experience of the study investigators.
28 August 2012	Recruitment to the study via General Practitioners was added to recruitment via psychiatrists. This was done in order to increase the number of trial patients.
03 February 2014	Modification of the duration of follow-up from a total of two years to a minimum of six months and maximum of 2 years. The rationale for this change was that recruitment had been very difficult and therefore we wished to maximise our potential to include participants. As a consequence, recruitment would be continued for a sufficient time period to reach the primary outcome of the study (namely the reduction in prolactin level), which, when achieved, occurs within six months of starting the study drug. There would be insufficient follow-up time to investigate changes in bone mineral density, the secondary outcome of the study. However, there would be no practical consequences, as in the study we found no patients actually requiring a bone mineral density scan after two years from baseline.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported