Clinical trial results:
Rationalisation of antipsychotic drug use in older people, using [18F]-Fallypride PET

Summary

EudraCT number	2011-005218-13
Trial protocol	GB
Global end of trial date	04 February 2016

Results information

Result version number	v1 (current)
This version publication date	04 September 2019
First version publication date	04 September 2019
Summary attachment (see zip file)	Final Report (EndofStudyreport_SR_24021.pdf)

Trial information

Trial identification

Sponsor protocol code	2167SR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01454453
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	Strand, London, United Kingdom, WC2R 2LS
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Scientific contact	Dr Suzanne Reeves, Kings College London, +44 2078480548, suzanne.j.reeves@kcl.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	04 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 February 2016
Global end of trial reached?	Yes
Global end of trial date	04 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

(i)To investigate differences in regional dopamine D2/3 receptor occupancy between Alzheimer's Disease, Schizophrenia Like Psychosis and Healthy Controls after 4 days treatment with amisulpride 50mg daily
(ii)To investigate differences in the threshold of dopamine D2/3 receptor occupancy required for 25% symptom reduction and emergence of motor side effects in SLP and AD during 4-10 weeks treatment with amisulpride (50-200mg daily)
(iii) To determine dose-response relationships (dose/plasma level/clinical outcome) in SLP and AD during dose-titration of amisulpride (50-200mg) over 4-10 weeks

Protection of trial subjects:

The safety profile of amisulpride will be determined through the use of scales that measure side effects and form part of the efficacy assessment (see above)
Evaluation will be carried out immediately prior to each dose increase (every 14+-7 days)

Background therapy:

None

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 March 2012
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	0
From 65 to 84 years	2
85 years and over	38

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from one clinical site within the UK between 2012 and 2015.

Pre-assignment

Screening details:

Patients with Schizophrenia-like psychosis with onset after 60 years or Alzheimers Disease who are aged between 60 and 95 years of age.

Period 1

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

Blinding implementation details:

No blinding

Arms

Arm title	Group 3 AD, SLP treated group

Arm description:

participants with Alzheimers Disease or Schizophrenia-like psychosis with onset after 60 years .

Arm type	Experimental
Investigational medicinal product name	Amisulpride 50mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Groupsd 3 (AD, SLP) will remain on a dose of 50mg daily until their next follow-up assessment (14±3 days). Follow-up assessment will be co-ordinated with clinical teams prescribing and will take place immediately prior to each dose increase (this will be determined by the prescribing clinician, the standard dose increment being 50mg at a time). Follow-up assessment will take place thereafter every 14±13 days, to coincide with each review by the prescribing team (which may be variable), over a total of 10 weeks. The maximum daily dose prescribed will be 200mg daily (taken as 100mg tablets twice daily).

Number of subjects in period 1	Group 3 AD, SLP treated group
Started	40
Completed	31
Not completed	9
Adverse event, serious fatal	1
Physician decision	1
Adverse event, non-fatal	2
Non-compliance with protocol	5

Baseline characteristics

Reporting groups	
Reporting group title	Group 3 AD, SLP treated group
Reporting group description: participants with Alzheimers Disease or Schizophrenia-like psychosis with onset after 60 years .	

Reporting group values	Group 3 AD, SLP treated group	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
Adults aged 60-69 years	2	2	
Adults aged 70 - 79 years	15	15	
Adults aged 80-89 years	19	19	
Adults aged 90 to 95 years	4	4	
Gender categorical Units: Subjects			
Female	25	25	
Male	15	15	

End points

End points reporting groups

Reporting group title	Group 3 AD, SLP treated group

Reporting group description:

participants with Alzheimers Disease or Schizophrenia-like psychosis with onset after 60 years .

Primary: Primary

End point title	Primary[1]

End point description:

To investigate the relationship between plasma levels and regional D2/3 receptor occupancy following steady state (4 days) treatment with a fixed dose (50mg) of amisulpride within 3 groups.
To investigate the relationship between plasma kinetics, regional D2/3 receptor occupancy and therapeutic and adverse effect profile in patients with SLP and AD (20 in each group) during 4-10 weeks treatment with amisulpride (50-200mg daily).
To combine data on clinical outcome and pharmacokinetics in patients with SLP and AD (40 in each group) during 4-10 weeks treatment with amisulpride (50-200mg daily).

End point type	Primary

End point timeframe:

Duration of trial - 0-70 days.

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: Please see attached document for results data.

End point values	Group 3 AD, SLP treated group			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Whole	31			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary

End point title	Secondary

End point description:

Secondary objective
To test the hypothesis that attentional/executive functioning will improve and motor speed decrease between baseline and end of dose-titration in the 2 patient groups (4-10 weeks).

(i) Change in neuropsychological test performance measures at the end of dose titration (4-12 weeks treatment with 50-200mg amisulpride) (groups 2 and 3)
(ii) Change in test performance measures over a 4 week period in the absence of treatment (group 4 & 5)

End point type	Secondary

End point timeframe:
0 to 70 days

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Duration of treatment - ie 0 to 70 dyas

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Treatment Group

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No adverse events were recorded

Serious adverse events	Treatment Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 39 (15.38%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Atrial Fibrilation			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fall			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Dehydrations			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
syndrome of inappropriate antidiuretic hormone secretion			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Low Blood Sugar			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2014	This amendment also includes a non-substantial amendments to the protocol (Version 3 16 Mar 12 and version 4.0 25 Oct 12) since the initial CTA approval for the study. The following was amended – Version 3 In the original protocol, there was no mention of contraindications to amisulpride; this is now included In the original protocol, the flowchart for group 1 did not include ECG screening; neither was it mentioned in the 'screening' section.; this is now included Version 4 As the study aims to use a two-scan approach to calculate occupancy between pre- and posttreatment scans; this approach will not be possible if a pre-treatment scan fails. In this situation, it is planned to estimate baseline dopamine D2/3 receptor BPND from the mean baseline BPND (age- and gender- corrected) of other participants from the same patient group during analysis. Prolactin levels during dose-titration and the steady state component of the study will be measured. This will not require any additional procedures, as prolactin levels will be obtained from the same sample tube used to measure amisulpride levels. Any references to Joint Clinical Trials Office changed to King's Health Partners Clinical Trials Office throughout the protocol Protocol has been amended clarify the SmPC as the study reference document and detail that a Developmental Safety Update Report will now be submitted in place of the Annual Safety Report.
19 March 2015	Additional blood sample to be taken prior to PET scanning to allow amisulpride binding to plasma proteins to be estimated, which will inform about the fraction of 'unbound drug' that is free to pass from peripheral bloodstream to the central nervous system (CNS). This information will be used to inform the pharmacokinetic (non-linear mixed effect) model for amisulpride.

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.

Groups 1 & 2 not recruited.
Trial terminated due to failure to recruit, powered on the basis of imaging & aimed to detect differences in the threshold occupancy for extrapyramidal side effects (EPS) during dose titration in the 2 patient groups.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28334978

http://www.ncbi.nlm.nih.gov/pubmed/27481049