# 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 |
| Public contact | Dr Suzanne Reeves, Kings College London, +44 2078480548, suzanne.j.reeves@kcl.ac.uk |
| Scientific contact | Dr Suzanne Reeves, Kings College London, +44 2078480548, suzanne.j.reeves@kcl.ac.uk |
| Sponsor organisation name | South London & Maudsley NHS Foundation Trust |
| Sponsor organisation address | Monks Orchard Road Beckenham , London, United Kingdom, BR3 3BX |
| Public contact | Dr Suzanne Reeves, South London & Maudsley NHS Foundation Trust, +44 2078480548, suzanne.j.reeves@kcl.ac.uk |
| Scientific contact | Dr Suzanne Reeves, South London & Maudsley NHS Foundation Trust, +44 2078480548, suzanne.j.reeves@kcl.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 | 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<br>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<br>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<br>and version 4.0 25 Oct 12) since the initial CTA approval for the study. The following was amended –<br>Version 3<br>In the original protocol, there was no mention of contraindications to amisulpride; this is now<br>included<br>In the original protocol, the flowchart for group 1 did not include ECG screening; neither was it<br>mentioned in the 'screening' section.; this is now included<br>Version 4<br>As the study aims to use a two-scan approach to calculate occupancy between pre- and posttreatment<br>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.<br>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.<br>Any references to Joint Clinical Trials Office changed to King's Health Partners Clinical Trials<br>Office throughout the protocol<br>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