



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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 09 April 2013 | <ul style="list-style-type: none">- 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