# Clinical trial results:
# Mirtazapine added to SSRIs for treatment resistant depression in primary care: a placebo controlled randomised controlled trial

## Summary

| | |
|---|---|
| EudraCT number | 2012-000090-23 |
| Trial protocol | GB |
| Global end of trial date | 19 December 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 14 March 2019 |
| First version publication date | 14 March 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | UoB1651 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | ISRCTN06653773 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | University of Bristol |
| Sponsor organisation address | One Cathedral Square, Bristol, United Kingdom, BS1 5DD |
| Public contact | Rachel Davies, University of Bristol, +44 1174284021 , rachel.davies@bristol.ac.uk |
| Scientific contact | Rachel Davies, University of Bristol, +44 1174284021 , rachel.davies@bristol.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 | 02 December 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 19 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To determine the effectiveness of the addition of the antidepressant mirtazapine to an SSRI or SNRI in reducing depressive symptoms and improving quality of life at 12 weeks, 24 weeks and 12 months (compared to the addition of a placebo).

Protection of trial subjects:

usual standard operating procedures in the event of disclosure of ideas of suicide or self harm.

Background therapy:

not applicable

Evidence for comparator:

not applicable

| | |
|---|---|
| Actual start date of recruitment | 26 August 2013 |
| 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: 480 |
| Worldwide total number of subjects | 480 |
| EEA total number of subjects | 480 |

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) | 406 |
| From 65 to 84 years | 74 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment took place from August 2013 to October 2015 in four centres, all in the United Kingdom

### Pre-assignment

Screening details:

751 patients assessed for eligibility
481 eligible, 270 ineligible (Not depressed)
480 randomised

### 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, Monitor, Data analyst |

Blinding implementation details:

The treatment allocation schedule was computer generated by a statistician independent of the trial team in a 1:1 ratio, stratified by centre and minimised by baseline depression score, sex and whether the participant was receiving a psychological intervention. Packs contained encapsulated mirtazapine 15mg or identical placebo.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Mirtazapine |

Arm description:

participants treated with the active medication

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Mirtazapine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants were asked to take one capsule daily for 2 weeks and then increase to 2 capsules daily thereafter

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Patients treated with placebo

| | |
|---|---|
| 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 were asked to take one capsule daily for 2 weeks and then increase to 2 capsules daily thereafter

| **Number of subjects in period 1** | Mirtazapine | Placebo |
|---|---|---|
| Started | 241 | 239 |
| Completed | 214 | 217 |
| Not completed | 27 | 22 |
| Lost to follow-up | 27 | 22 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Mirtazapine |
| Reporting group description: participants treated with the active medication | |
| Reporting group title | Placebo |
| Reporting group description: Patients treated with placebo | |

| Reporting group values | Mirtazapine | Placebo | Total |
|---|---|---|---|
| Number of subjects | 241 | 239 | 480 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 197 | 209 | 406 |
| From 65-84 years | 44 | 30 | 74 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| geometric mean | 50.4 | 49.9 | |
| standard deviation | ± 13.8 | ± 12.5 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 168 | 164 | 332 |
| Male | 73 | 75 | 148 |
| Baseline Beck Depression Inventory Score<br>Units: Subjects | | | |
| 14-25 | 77 | 79 | 156 |
| 26-34 | 78 | 78 | 156 |
| >34 | 86 | 82 | 168 |
| ICD-10 Diagnosis of Depression<br>Units: Subjects | | | |
| mild | 38 | 44 | 82 |
| moderate | 138 | 144 | 282 |
| severe | 65 | 51 | 116 |
| Mean BDI score<br>Units: scale 0-63 | | | |
| geometric mean | 31.5 | 30.6 | |
| standard deviation | ± 10.2 | ± 9.6 | - |
| General Anxiety Disorder (GAD7)<br>Units: scale 0-21 | | | |

| | | | |
|---|---|---|---|
| geometric mean | 11.3 | 10.7 | |
| standard deviation | ± 4.8 | ± 4.8 | - |

## End points

| End points reporting groups | |
|---|---|
| Reporting group title | Mirtazapine |
| Reporting group description:<br>participants treated with the active medication | |
| Reporting group title | Placebo |
| Reporting group description:<br>Patients treated with placebo | |

| Primary: mean BDI score | |
|---|---|
| End point title | mean BDI score |
| End point description: | |
| End point type | Primary |
| End point timeframe:<br>12 weeks | |

| End point values | Mirtazapine | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 214 | 217 | | |
| Units: scale 0-63 | | | | |
| geometric mean (standard deviation) | 18 (± 12.3) | 19.7 (± 12.4) | | |

### Statistical analyses

| Statistical analysis title | Change in mean BDI score analysed as a continuous |
|---|---|
| Comparison groups | Mirtazapine v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.09 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.92 |
| upper limit | 0.27 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs were reported from the time a signed and dated informed consent form was obtained until completion of the last trial related procedure (collection of follow-up data 12 months after randomisation)

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | SMPC and BNF |
| Dictionary version | latest |

### Reporting groups

| | |
|---|---|
| Reporting group title | Mirtazapine group |

Reporting group description:

Participants randomised to Mirtazapine

| | |
|---|---|
| Reporting group title | Placebo group |

Reporting group description:

Participants randomised to placebo

| Serious adverse events | Mirtazapine group | Placebo group | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 241 (3.32%) | 3 / 239 (1.26%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Ischaemia | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 239 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 239 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Dental care | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 239 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Reproductive system and breast disorders | | | |
| Hysterectomy | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 239 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 239 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| chest infection | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 239 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 2 / 241 (0.83%) | 0 / 239 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| trauma | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 2 / 239 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| infected ulcer | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 239 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Mirtazapine group | Placebo group | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 180 / 241 (74.69%) | 89 / 239 (37.24%) | |
| Nervous system disorders | | | |
| psychiatric | Additional description: This includes drowsiness, headache, TIA, unpleasant dreams, sleep disturbance | | |
| subjects affected / exposed | 70 / 241 (29.05%) | 27 / 239 (11.30%) | |
| occurrences (all) | 70 | 27 | |
| General disorders and administration site conditions | | | |
| see below | Additional description: includes anticholinergic effects, allergic reactions, minor endocrine, ENT, Dental, dermatological, ophthalmological, haematological and infective disorders | | |
| subjects affected / exposed | 27 / 241 (11.20%) | 26 / 239 (10.88%) | |
| occurrences (all) | 27 | 26 | |
| Gastrointestinal disorders | | | |
| Appetite disorder | Additional description: this includes appetite changes, nausea and weight gain | | |
| subjects affected / exposed | 34 / 241 (14.11%) | 18 / 239 (7.53%) | |
| occurrences (all) | 34 | 18 | |
| Reproductive system and breast disorders | | | |
| minor disorders | | | |
| subjects affected / exposed | 2 / 241 (0.83%) | 1 / 239 (0.42%) | |
| occurrences (all) | 2 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| minor respiratory disorders | | | |
| subjects affected / exposed | 6 / 241 (2.49%) | 3 / 239 (1.26%) | |
| occurrences (all) | 6 | 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| minor injury | | | |
| subjects affected / exposed | 15 / 241 (6.22%) | 17 / 239 (7.11%) | |
| occurrences (all) | 15 | 17 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/30442772