



Clinical trial results:

A Proof of Principle, Double-Blind, Randomised Placebo-Controlled, Multi-centre Trial of pravaStatin to Ameliorate Early Onset Pre-eclampsia Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2009-012968-13 |
| Trial protocol | GB |
| Global end of trial date | 09 September 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 12 July 2018 |
| First version publication date | 12 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | UCL08/0350 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN23410175 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University College London |
| Sponsor organisation address | 149 Tottenham Court Road, London, United Kingdom, W1T 7DN |
| Public contact | Anne Downey, University College London, a.downey@ucl.ac.uk |
| Scientific contact | Anne Downey, University College London, a.downey@ucl.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 | 22 December 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 August 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 September 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The aim of the trial is to establish whether pravastatin will lead to a significant reduction of circulating anti-angiogenic factors in women with early-onset pre-eclampsia. To test this hypothesis, we will ask the following questions:

1. Does pravastatin cause a greater inhibition of circulating anti-angiogenic factors in women with early-onset pre-eclampsia compared with placebo?
2. Are there any beneficial or adverse clinical effects to the mother or the baby following gestational exposure to pravastatin?
3. If pravastatin appears to safely inhibit circulating anti-angiogenic factors, how best can a substantive trial/health technology assessment be undertaken to develop guidance for routine use of statins to prevent or ameliorate pre-eclampsia?

Protection of trial subjects:

No specific measures

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 18 June 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: 62 |
| Worldwide total number of subjects | 62 |
| EEA total number of subjects | 62 |

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) | 62 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited and randomised into the trial on the 18-Jun-2011 and the last patient was randomised into the trial on 30-Jun-2014.

The study was open in the UK only and was open in 16 centres.

Pre-assignment

Screening details:

There were 388 women screened in order to randomise 62 women.

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, Assessor |

Blinding implementation details:

Overencapsulated IMP and matching placebo

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-------------|
| Arm title | Pravastatin |
|------------------|-------------|

Arm description:

Pravastatin

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Pravastatin |
| Investigational medicinal product code | IMP1 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

40mg daily until delivery

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

Arm description:

Placebo

| | |
|--|---------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Daily until delivery

| Number of subjects in period 1 | Pravastatin | Placebo |
|---------------------------------------|-------------|---------|
| Started | 30 | 32 |
| Completed | 30 | 32 |

Baseline characteristics

Reporting groups

| | |
|---|-------------|
| Reporting group title | Pravastatin |
| Reporting group description: Pravastatin | |
| Reporting group title | Placebo |
| Reporting group description: Placebo | |

| Reporting group values | Pravastatin | Placebo | Total |
|--|-------------|---------|-------|
| Number of subjects | 30 | 32 | 62 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults | 30 | 32 | 62 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 32.4 | 30.4 | |
| standard deviation | ± 5.6 | ± 6.3 | - |
| Gender categorical | | | |
| Sex, as subjects all pregnant | | | |
| Units: Subjects | | | |
| Female | 30 | 32 | 62 |
| Male | 0 | 0 | 0 |
| Gestational age at diagnosis | | | |
| Gestational age of fetus, in weeks, at diagnosis of severe pre-eclampsia. Eligible if <32+6 weeks. | | | |
| Units: Subjects | | | |
| <30 weeks | 23 | 24 | 47 |
| >= 30 weeks | 7 | 8 | 15 |
| Smoking status at diagnosis | | | |
| Self-declared smoking status | | | |
| Units: Subjects | | | |
| Smoker | 2 | 1 | 3 |
| Stopped smoking when became pregnant | 1 | 1 | 2 |
| Non-smoker | 27 | 30 | 57 |
| Severity of pre-eclampsia at randomisation | | | |
| All Using internationally recognised standard definitions, two categories of severity were defined: 1. Blood pressure >140mmHg systolic or 90mmHg diastolic but <160mmHg and <110mmHg respectively 2. Blood pressure ≥160mmHg systolic or 110mmHg diastolic | | | |
| Units: Subjects | | | |
| Blood pressure >140mmHg systolic or 90mmHg diastol | 13 | 14 | 27 |
| Blood pressure ≥160mmHg systolic or 110mmHg diasto | 17 | 18 | 35 |

Subject analysis sets

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Pravastatin |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

All subjects analysed according to the arm to which they were randomised, regardless of compliance.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Placebo |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

All subjects analysed according to the arm to which they were randomised, regardless of compliance.

| Reporting group values | Pravastatin | Placebo | |
|--|-------------|---------|--|
| Number of subjects | 30 | 32 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults | 62 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 32.4 | 30.4 | |
| standard deviation | ± 5.6 | ± 6.3 | |
| Gender categorical | | | |
| Sex, as subjects all pregnant | | | |
| Units: Subjects | | | |
| Female | 30 | 32 | |
| Male | 0 | 0 | |
| Gestational age at diagnosis | | | |
| Gestational age of fetus, in weeks, at diagnosis of severe pre-eclampsia. Eligible if <32+6 weeks. | | | |
| Units: Subjects | | | |
| <30 weeks | 23 | 24 | |
| >= 30 weeks | 7 | 8 | |
| Smoking status at diagnosis | | | |
| Self-declared smoking status | | | |
| Units: Subjects | | | |
| Smoker | 2 | 1 | |
| Stopped smoking when became pregnant | 1 | 1 | |
| Non-smoker | 27 | 30 | |
| Severity of pre-eclampsia at randomisation | | | |
| All | | | |
| Using internationally recognised standard definitions, two categories of severity were defined: | | | |
| 1. Blood pressure >140mmHg systolic or 90mmHg diastolic but <160mmHg and <110mmHg respectively | | | |
| 2. Blood pressure ≥160mmHg systolic or 110mmHg diastolic | | | |
| Units: Subjects | | | |
| Blood pressure >140mmHg systolic or 90mmHg diastol | 13 | 14 | |
| Blood pressure ≥160mmHg systolic or 110mmHg diasto | 17 | 18 | |

End points

End points reporting groups

| | |
|-----------------------------------|---|
| Reporting group title | Pravastatin |
| Reporting group description: | Pravastatin |
| Reporting group title | Placebo |
| Reporting group description: | Placebo |
| Subject analysis set title | Pravastatin |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | All subjects analysed according to the arm to which they were randomised, regardless of compliance. |
| Subject analysis set title | Placebo |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | All subjects analysed according to the arm to which they were randomised, regardless of compliance. |

Primary: sFLT-1

| | |
|------------------------|----------------------------------|
| End point title | sFLT-1 |
| End point description: | |
| End point type | Primary |
| End point timeframe: | First 3 days after randomisation |

| End point values | Pravastatin | Placebo | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 ^[1] | 29 ^[2] | | |
| Units: ng/ml | | | | |
| arithmetic mean (standard deviation) | 8.52 (± 4.8) | 12.24 (± 6.39) | | |

Notes:

[1] - Number of subjects providing at least 1 sample/ datapoint

[2] - Number of subjects providing at least 1 sample/ datapoint

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Primary analysis |
| Comparison groups | Placebo v Pravastatin |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Regression, Logistic |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.29 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.17 |
| upper limit | 0.6 |
| Variability estimate | Standard deviation |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of trial treatment to 6 weeks post-delivery

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 11 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Pravastatin |
|-----------------------|-------------|

Reporting group description:

Pravastatin

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

Reporting group description:

Placebo

| Serious adverse events | Pravastatin | Placebo | |
|---|---|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 30 (16.67%) | 5 / 29 (17.24%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Hypertensive emergency | Additional description: Uncontrolled and/or exacerbation of hypertension | | |
| subjects affected / exposed | 3 / 30 (10.00%) | 3 / 29 (10.34%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Haemorrhage in pregnancy | Additional description: Antepartum haemorrhage requiring Caesarean delivery | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Liver function test abnormal subjects affected / exposed | 0 / 30 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Postpartum neurosis | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Postpartum sepsis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Pravastatin | Placebo | |
|--|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 30 (13.33%) | 9 / 29 (31.03%) | |
| Vascular disorders | | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 4 / 29 (13.79%) | |
| occurrences (all) | 2 | 4 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |

| | | | |
|---|---------------------|----------------------|--|
| Photopsia subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 2 / 29 (6.90%) 0 | |
| Gastrointestinal disorders | | | |
| Vomiting in pregnancy subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 3 / 29 (10.34%) 3 | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 5 / 29 (17.24%) 0 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 3 / 29 (10.34%) 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 29 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--------------------------------------|
| 05 January 2011 | Version 3.1 from AM01 (modification) |
| 22 November 2011 | Version 4.0 from AM02 |
| 16 April 2012 | Version 5.0 from AM03 |
| 19 July 2012 | Version 6.0 from AM04 |
| 18 January 2013 | Version 7.0 from AM05 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported