



Clinical trial results:

Is cessation of clopidogrel therapy associated with rebound of platelet activity in stable vascular disease patients?

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2007-007638-21 |
| Trial protocol | GB |
| Global end of trial date | 24 July 2012 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 19 August 2018 |
| First version publication date | 19 August 2018 |

Trial information

Trial identification

| | |
|-----------------------|-----|
| Sponsor protocol code | CR2 |
|-----------------------|-----|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN77887299 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|-------------------------------------------------------------------------------------------------|
| Sponsor organisation name | NHS Grampian |
| Sponsor organisation address | R&D Office, Foresterhill House Annexe, Aberdeen, United Kingdom, AB25 2ZB |
| Public contact | Gail Holland, NHS Grampian, 01224 555076, researchgovernance@abdn.ac.uk |
| Scientific contact | Gail Holland, NHS Grampian, 01224 555076, researchgovernance@abdn.ac.uk |
| Sponsor organisation name | University of Aberdeen |
| Sponsor organisation address | R&D Office, Foresterhill House Annexe, Aberdeen, United Kingdom, AB25 2ZB |
| Public contact | Professor Julie Brittenden, University of Aberdeen, 01224 551123, researchgovernance@abdn.ac.uk |
| Scientific contact | Professor Julie Brittenden, University of Aberdeen, 01224 551123, researchgovernance@abdn.ac.uk |

Notes:

Paediatric regulatory details

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|----------------------------------------------------------------------|----|
| 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 | 24 January 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 July 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 July 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary aim of this study is to identify whether there is evidence for a "rebound" effect on platelet markers associated with cessation of clopidogrel therapy. We propose to address this in patients with stable cardiovascular disease by means of a mechanistic study.

Protection of trial subjects:

Ethical approval was obtained (NOSRES 08/S0801/087), and each patient gave written informed consent.

Background therapy:

The thienopyridine derivative, clopidogrel is an effective inhibitor of platelet activation and aggregation as a result of its selective and irreversible blockade of the P2Y₁₂ receptor¹. Combination antiplatelet therapy with clopidogrel and aspirin has been shown to be an effective strategy in patients with acute coronary syndromes and in those undergoing percutaneous interventions.

Evidence for comparator:

A placebo group is included to determine whether any detected change in platelet activation is due to the clopidogrel therapy rather than changes that may occur over the course of the study in this population of patients.

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| Actual start date of recruitment | 08 October 2010 |
| 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: 172 |
| Worldwide total number of subjects | 172 |
| EEA total number of subjects | 172 |

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) | 75 |
| From 65 to 84 years | 97 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients who meet the criteria of the study will be identified from clinical databases of patients with stable vascular disease who have formerly attended the Cardiology and Vascular Surgery Unit at Aberdeen Royal Infirmary (ARI).

Pre-assignment

Screening details:

Participants will be invited by letter with information sheet enclosed. Prepaid envelope will be included to facilitate a reply. Those who reply positively will be offered an appointment by telephone by the research nurse and an opportunity to ask questions about the study.

Period 1

| | |
|------------------------------|-----------------------------------------|
| Period 1 title | Clopidogrel vs Placebo (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Clopidogrel |

Arm description: -

| | |
|----------------------------------------|--------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Clopidogrel |
| Investigational medicinal product code | |
| Other name | Plavix |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

75 mg daily for 30 days (containing Clopidogrel tablets 75mg diluted with Lactose PhEur enclosed in a hard capsule shell).

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

Dosage and administration details:

75mg daily for 30 days (containing Lactose PhEur 540mg to match the active)

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

Arm description: -

| | |
|-----------------------------------------------------------|---------|
| Arm type | Placebo |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Clopidogrel | Placebo |
|---------------------------------------|-------------|---------|
| Started | 88 | 84 |
| Completed | 88 | 84 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Clopidogrel vs Placebo |
|-----------------------|------------------------|

Reporting group description: -

| Reporting group values | Clopidogrel vs Placebo | Total | |
|----------------------------------------------------|------------------------|-------|--|
| Number of subjects | 172 | 172 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 75 | 75 | |
| From 65-84 years | 97 | 97 | |
| 85 years and over | 0 | 0 | |
| Gender categorical Units: Subjects | | | |
| Female | 84 | 84 | |
| Male | 88 | 88 | |

End points

End points reporting groups

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

Primary: ADP -stimulated platelet fibrinogen binding

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|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| End point title | ADP -stimulated platelet fibrinogen binding |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Blood samples were taken at pre-treatment baseline, on treatment just before discontinuation of study drug, and on days 7, 14, and 28 after discontinuation. | |

| End point values | Clopidogrel | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 84 | | |
| Units: 10 umol/l | | | | |
| number (not applicable) | 88 | 84 | | |

Statistical analyses

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Statistical analysis title | Final Results |
| Statistical analysis description: | |
| Descriptive results were produced for all outcomes, but statistical testing was only performed for the primary and secondary outcomes. The primary research question was addressed using a mixed model procedure, xt-mixed in Stata (21), using 7 models, 1 for each primary and secondary outcome measure, excluding the on-treatment timepoint but including baseline and 7, 14, and 28 days after treatment. | |
| Comparison groups | Clopidogrel v Placebo |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Mixed models analysis |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 24hrs.

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

Dictionary used

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|-----------------|------|
| Dictionary name | None |
|-----------------|------|

| | |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Total AE |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events | Total AE | | |
|---------------------------------------------------|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 81 (3.70%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Cardiac disorders | | | |
| Chest pain | | | |
| subjects affected / exposed ^[1] | 1 / 1 (100.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest tightness | | | |
| subjects affected / exposed ^[2] | 1 / 1 (100.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Vasovagal | | | |
| subjects affected / exposed ^[3] | 1 / 1 (100.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Figures added are accurate to the event.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Figures added are accurate to the event.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Figures added are accurate to the event.

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

| Non-serious adverse events | Total AE | | |
|-------------------------------------------------------|------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 47 / 81 (58.02%) | | |
| Cardiac disorders | | | |
| Tightness in gullet/chest | | | |
| subjects affected / exposed ^[4] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed ^[5] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Angina unstable | | | |
| subjects affected / exposed ^[6] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Chest pain | | | |
| subjects affected / exposed ^[7] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Myocardial infarction | Additional description: Mild | | |
| subjects affected / exposed ^[8] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Irregular heart beat | | | |
| subjects affected / exposed ^[9] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Tooth infection | | | |
| subjects affected / exposed ^[10] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Neck pain | | | |
| subjects affected / exposed ^[11] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Shoulder pain | | | |
| subjects affected / exposed ^[12] | 3 / 3 (100.00%) | | |
| occurrences (all) | 3 | | |
| Bruising | | | |

| | | | |
|---------------------------------------------|-----------------|--|--|
| subjects affected / exposed ^[13] | 6 / 6 (100.00%) | | |
| occurrences (all) | 6 | | |
| Thigh pain | | | |
| subjects affected / exposed ^[14] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Increased sweats | | | |
| subjects affected / exposed ^[15] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| swelling of polypoidas | | | |
| subjects affected / exposed ^[16] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Tiredness | | | |
| subjects affected / exposed ^[17] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Knee pain | | | |
| subjects affected / exposed ^[18] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Sore foot | | | |
| subjects affected / exposed ^[19] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Arm pain | | | |
| subjects affected / exposed ^[20] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Back pain | | | |
| subjects affected / exposed ^[21] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| redness in ear | | | |
| subjects affected / exposed ^[22] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Bad Tempered | | | |
| subjects affected / exposed ^[23] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Increased hot flushes | | | |
| subjects affected / exposed ^[24] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |

| | | | |
|------------------------------------------------------------------------------------------------------------|----------------------|--|--|
| Epistaxis subjects affected / exposed ^[25] occurrences (all) | 5 / 5 (100.00%) 5 | | |
| Increased bleeding subjects affected / exposed ^[26] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Vasovagul subjects affected / exposed ^[27] occurrences (all) | 1 / 3 (33.33%) 3 | | |
| Immune system disorders Common Cold subjects affected / exposed ^[28] occurrences (all) | 8 / 8 (100.00%) 8 | | |
| Cold sore subjects affected / exposed ^[29] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Viral illness subjects affected / exposed ^[30] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| sore throat subjects affected / exposed ^[31] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Eye disorders Blood shot eye subjects affected / exposed ^[32] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed ^[33] occurrences (all) | 3 / 3 (100.00%) 3 | | |
| Dyspepsia subjects affected / exposed ^[34] occurrences (all) | 4 / 4 (100.00%) 4 | | |
| Phlebitis subjects affected / exposed ^[35] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Stomach upset | | | |

| | | | |
|------------------------------------------------------------------------------------------------------------------------------|----------------------|--|--|
| subjects affected / exposed ^[36] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Diverticulitis subjects affected / exposed ^[37] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| acid reflux subjects affected / exposed ^[38] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Diarrhoea and vomiting subjects affected / exposed ^[39] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Vomiting subjects affected / exposed ^[40] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed ^[41] occurrences (all) | 2 / 2 (100.00%) 2 | | |
| Worsening of COPD subjects affected / exposed ^[42] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Skin and subcutaneous tissue disorders Itchy skin subjects affected / exposed ^[43] occurrences (all) | 2 / 2 (100.00%) 2 | | |
| Renal and urinary disorders Urinary tract infection subjects affected / exposed ^[44] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Endocrine disorders Diabetes mellitus subjects affected / exposed ^[45] occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Musculoskeletal and connective tissue disorders Increased arthritis pain | | | |

| | | | |
|---------------------------------------------|-----------------|--|--|
| subjects affected / exposed ^[46] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Anus infection | | | |
| subjects affected / exposed ^[47] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Chest infection | | | |
| subjects affected / exposed ^[48] | 4 / 4 (100.00%) | | |
| occurrences (all) | 4 | | |
| Infection | | | |
| subjects affected / exposed ^[49] | 2 / 2 (100.00%) | | |
| occurrences (all) | 2 | | |
| Infected bursitis | | | |
| subjects affected / exposed ^[50] | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |

Notes:

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Figures added are accurate to the event.

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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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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|--------------------------------------------------------------------------------------------------------------------------------------------|
| The main limitation of the present study was that patients received clopidogrel for only 1 month, so chronic changes may have been missed. |
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24211510>