# Clinical trial results:
# Evaluating the benefit of additional platelet inhibition in acute coronary syndrome patients with high platelet reactivity undergoing PCI

## Summary

| | |
|---|---|
| EudraCT number | 2010-020219-35 |
| Trial protocol | GB DE |
| Global end of trial date | 17 October 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 16 October 2019 |
| First version publication date | 16 October 2019 |
| Summary attachment (see zip file) | APACS publication (APACS Publication.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 2011CI007H |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Royal Brompton & Harefield NHS Trust |
| Sponsor organisation address | Sydney Street, London, United Kingdom, SW3 6NP |
| Public contact | Dr. Tobias Geisler<br>Medizinische Klinik III, Department of Cardiology and Cardiovascular disease,<br>, Dr. Tobias Geisler<br>Medizinische Klinik III, Department of Cardiology and Cardiovascular disease,<br>, 0049 70712983688, tobias.geisler@med.uni-tuebingen.de |
| Scientific contact | Dr. Miles Dalby<br>Harefield Hospital<br>Hill End Road, Harefield<br>Middlesex UB9 6JH<br>United Kingdom<br>, Dr. Miles Dalby<br>Harefield Hospital<br>Hill End Road, Harefield<br>Middlesex UB9 6JH<br>United Kingdom<br>, 0044 1895 828990, m.dalby@rbht.nhs.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 | 16 April 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 October 2013 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Main objective of the trial:
OBSERVATIONAL REGISTRY OF SCREENED PATIENTS
To identify the proportion of patients who are good responders to routine doses of Clopidogrel and compare the events of death at 30 days.
RANDOMISED PATIENTS
To evaluate if reloading with Prasugrel compared to a high dose regimen of Clopidogrel results in more patients having a low platelet reactivity. Patients will be identified who have poor platelet response to previous Clopidogrel and have undergone an invasive procedure (PCI) to treat their narrowed or blocked heart vessels.
SUBSTUDIES
1. Title: APACS-HPR genetic substudy
To determine the relevant influence of genetic heritage on response variability to the Clopidogrel and Prasugrel antiplatelet treatment.
2) Title: APACS-HPR biomarker substudy
To determine the variability of platelet inhibition to Clopidogrel or Prasugrel treatment if this is influenced by the inflammatory condition and the extent of platelet activation and blood flow to the

Protection of trial subjects:

The APACS trial included patients with known coronary artery anatomy pre-planned PCI clinically. Therefore, the prasugrel loading and maintenance dosing regimen was consistent with standard prescribing guidelines.
At the time there was no evidence and no consistent recommendation on how to treat ACS patients who have been pretreated
with clopidogrel and who are poor responders. It was belived at the time that these patients may have been exposed to increased bleeding risk by re-loading them with prasugrel, however these patients benefited from preselection of patients with high platelet reactivity (i.e. poor responders) by reduction of ischemic rather than increase in bleeding risk.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 15 February 2012 |
| 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 | Germany: 38 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Worldwide total number of subjects | 44 |
| EEA total number of subjects | 44 |

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) | 30 |
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study started enrolment in 15 February 2012 and recruitment terminated on the 31st July 2013 well before the predicted recruiting time, so that only 44 patients could be recruited.

### Pre-assignment

Screening details:

Screening details:
Patients admitted to the hospital with suspected ACS (unstable angina, NSTEMI or STEMI) requiring PCI were screened. A study blood sample was required at least 2 hours after prior loading with clopidogrel to evaluate platelet activity. If this was not achievable for clinical reasons then this patient would not be eligible for

### Period 1

| | |
|---|---|
| Period 1 title | TP 0 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Clopidogrel |

Arm description:

Group 1: Clopidogrel (Plavix)
• Day 1 Loading 600mg
• Day 2 to 7 day: 150mg o.d.
• Day 8 to 30 days: 75mg o.d.

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

Dosage and administration details:

Day 1 loading 60mg
Day 2 to 7 10mg o.d.
Day 8 to 30 days 10mg od

| **Number of subjects in period 1** | Clopidogrel |
|---|---|
| Started | 44 |
| Completed | 44 |

## Period 2

| | |
|---|---|
| Period 2 title | TP 1 to TP 6 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

## Arms

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

Arm description:

Day 1 loading 60mg
Day 2 to 7 10mg o.d.
Day 8 to 30 days 10mg od

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Prasugrel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Day 1 loading 60mg
• Day 2 to 7 10mg o.d.
• Day 8 to 30 days 10mg od

| | |
|---|---|
| **Arm title** | Clopidogrel (Plavix) |

Arm description:

Day 1 Loading 600mg
Day 2 to 7 day: 150mg o.d.
Day 8 to 30 days: 75mg o.d.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Clopidogrel (Plavix) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Day 1 Loading 600mg
Day 2 to 7 day: 150mg o.d.
Day 8 to 30 days: 75mg o.d.

| **Number of subjects in period 2** | Prasugrel | Clopidogrel (Plavix) |
|---|---|---|
| Started | 22 | 22 |
| Completed | 22 | 22 |

## Baseline characteristics

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Clopidogrel |
| Reporting group description: | |
| Group 1: Clopidogrel (Plavix)<br>• Day 1 Loading 600mg<br>• Day 2 to 7 day: 150mg o.d.<br>• Day 8 to 30 days: 75mg o.d. | |
| Reporting group title | Prasugrel |
| Reporting group description: | |
| Day 1 loading 60mg<br>Day 2 to 7 10mg o.d.<br>Day 8 to 30 days 10mg od | |
| Reporting group title | Clopidogrel (Plavix) |
| Reporting group description: | |
| Day 1 Loading 600mg<br>Day 2 to 7 day: 150mg o.d.<br>Day 8 to 30 days: 75mg o.d. | |

### Primary: decreased platelet reactivity under the cut-off value of 400 Au.min

| | |
|---|---|
| End point title | decreased platelet reactivity under the cut-off value of 400 Au.min |
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| decreased platelet reactivity under the cut-off value of 400 Au.min in the prasugrel re-loading arm compared to the clopidogrel re-loading arm at 4 hours after loading with study drug in patients with initial high platelet reactivity | |

| End point values | Prasugrel | Clopidogrel (Plavix) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: 400 Au.min | | | | |
| number (not applicable) | 22 | 22 | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical Analysis |
| Statistical analysis description: | |
| Baseline variables were compared with the use of chi-square tests for categorical variables; t-tests or the Wilcoxon rank-sum were used for continuous variables depending on the distributions of the variables. Comparison of the primary endpoint and secondary endpoints was carried out using a chi squared or Fishers exact test. The confidence intervals were two-sided with a 95% confidence level, and all hypothesis tests were two-sided carried out at a significance level $p < 0.05$. | |
| Comparison groups | Clopidogrel (Plavix) v Prasugrel |

| | |
|---|---|
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 |
| Method | Chi-squared corrected |
| Parameter estimate | difference in proportions |
| Point estimate | 0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.48 |
| upper limit | 0.66 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Adverse Events reported on CRF and hospital notes in timely manner | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15 |

| Reporting groups | |
|---|---|
| Reporting group title | Prasugrel |

Reporting group description: -

| Serious adverse events | Prasugrel | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Prasugrel | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| Cardiac disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 30 June 2011 | Protocol Version 6, 23rd May; Changes to the study protocol as requested by BPharm. |
| 29 February 2012 | NOSA 2 – addition of 3 new sites. Data Custodianship changed.<br>Non-substantial amendment 01 – change to sponsor contact person from Wendy Butcher to Angela Cooper.<br>NOSA02 also includes delayed submission of NOSA01 to the MHRA (this is dated 24th January 2012) |
| 29 October 2012 | Protocol version 7/16 October 2012<br>PIS Version 5/16 October 2012;<br>This amendment was never implemented. The REC was informed that this amendment was 'voided' due to new safety information in relation to Prasugrel. PIS V5.0 was approved as part of this amendment. However the CI decided that the amendment of the PIS was not required due to the changes subsequently made and implemented with SA04. Version 4.0 is the latest version of the PIS as approved with SA01. |
| 09 January 2013 | Protocol 8/09 January 2013;<br>To 'void' SA03 – Protocol V7.0 was not in use all changes transferred to Protocol V8.0 submitted with this amendment as detailed |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 31 July 2013 | The study was terminated early as clopidogrel use decreased sharply due to introduction of newer P2Y12 inhibitors | - |

Notes:

### Limitations and caveats

None reported