



## Clinical trial results:

**A study of very low dose twice-daily compared to standard low dose once-daily aspirin following acute coronary syndromes - WILL IOWer dose aspirin be more effective following ACS?**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-000920-25 |
| Trial protocol           | GB             |
| Global end of trial date | 30 March 2017  |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 07 November 2018 |
| First version publication date | 07 November 2018 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | STH19177 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02741817 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Sheffield Teaching Hospitals NHS FT  |
| Sponsor organisation address | Glossop Road, Sheffield, United Kingdom, S10 2JF   |
| Public contact               | Clinical Research Office, Sheffield Teaching Hospitals NHS Foundation Trust, 0114 2712763, ResearchAdministration@sth.nhs.uk |
| Scientific contact           | Prof Rob Storey, Sheffield Teaching Hospitals NHS Foundation Trust, r.f.storey@sheffield.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                       | 30 April 2017 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 30 March 2017 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 March 2017 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The principal objective of this study is to assess the effects of two aspirin regimens (very low dose twice daily or standard low dose once daily) on the levels of thromboxane and prostacyclin, substances relevant to platelet activity, measured as their breakdown products in blood and urine, in patients on dual antiplatelet therapy for acute coronary syndromes (heart attacks and severe 'unstable' angina).

Protection of trial subjects:

Study participants were asked to take a lower dose of aspirin than usual for 14 days within the study. The patients to be studied were already on established on standard doses of aspirin and ticagrelor for acute coronary syndromes (ACS), and enough into the treatment period to be in a stable phase and therefore to minimise any additional risk.

The REC approved protocol was followed as well as local SOPs.

The IMP dose and bleeding times were kept to the minimum to answer the outcome measure.

Background therapy:

Not applicable as there was no requirements for the patient to be on any other drugs.

Evidence for comparator:

Aspirin 75mg once daily represents guideline directed standard therapy.

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 28 June 2016 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Worldwide total number of subjects   | 20                 |
| EEA total number of subjects         | 20                 |

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)      | 10 |
| From 65 to 84 years       | 10 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment period: 20/06/2016 to 01/12/2016.

Participants were recruited from England at one site in Sheffield.

### Pre-assignment

Screening details:

Number of subjects screened: 216

Screening enrollment criteria

Male or female aged over 18 years

Diagnosis of acute coronary syndrome greater than 30 days and less than 10 months

Receiving dual antiplatelet therapy with aspirin 75 mg once daily and ticagrelor 90 mg twice daily

### Pre-assignment period milestones

|                            |    |
|----------------------------|----|
| Number of subjects started | 20 |
|----------------------------|----|

|                              |    |
|------------------------------|----|
| Number of subjects completed | 20 |
|------------------------------|----|

### Period 1

|                |  |
|----------------|--|
| Period 1 title | Study medication period (overall period) |
|----------------|--|

|                              |     |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

|                   |                         |
|-------------------|-------------------------|
| Allocation method | Randomised - controlled |
|-------------------|-------------------------|

|               |             |
|---------------|-------------|
| Blinding used | Not blinded |
|---------------|-------------|

Blinding implementation details:

Not applicable

### Arms

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

|           |            |
|-----------|------------|
| Arm title | Sequence 1 |
|-----------|------------|

Arm description:

Aspirin 20mg twice daily for 14 days and Ticagrelor 90mg twice daily for 14 days

Followed by Aspirin 75mg once daily for 14 days and Ticagrelor 90mg twice daily for 14 days

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Aspirine lysine |
|--|-----------------|

|  |  |
|--|--|
| Investigational medicinal product code |  |
|--|--|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |                                    |
|----------------------|------------------------------------|
| Pharmaceutical forms | Powder for oral solution in sachet |
|----------------------|------------------------------------|

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

20mg twice daily or 75mg twice daily

|           |            |
|-----------|------------|
| Arm title | Sequence 2 |
|-----------|------------|

Arm description:

Aspirin 75mg twice daily for 14 days and Ticagrelor 90mg twice daily for 14 days

Followed by Aspirin 20mg once daily for 14 days and Ticagrelor 90mg twice daily for 14 days

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                                    |
|--|------------------------------------|
| Investigational medicinal product name | Aspirine lysine                    |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Powder for oral solution in sachet |
| Routes of administration               | Oral use                           |

Dosage and administration details:

20mg twice daily or 75mg twice daily

| <b>Number of subjects in period 1</b> | Sequence 1 | Sequence 2 |
|---------------------------------------|------------|------------|
| Started                               | 10         | 10         |
| Visit 1 -14 days                      | 10         | 10         |
| Visit 2 - 28 days                     | 10         | 10         |
| Visit 3 - 42 days                     | 10         | 10         |
| Completed                             | 10         | 10         |

## Baseline characteristics

### Reporting groups

|                                |                         |
|--------------------------------|-------------------------|
| Reporting group title          | Study medication period |
| Reporting group description: - |                         |

| Reporting group values                             | Study medication period | Total |  |
|--|-------------------------|-------|--|
| Number of subjects                                 | 20                      | 20    |  |
| Age categorical<br>Units: Subjects                 |                         |       |  |
| In utero   |                         | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) |                         | 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)                               |                         | 0     |  |
| From 65-84 years                                   |                         | 0     |  |
| 85 years and over                                  |                         | 0     |  |
| Age continuous<br>Units: years                     |                         |       |  |
| arithmetic mean                                    | 64.3                    |       |  |
| standard deviation                                 | ± 11.9                  | -     |  |
| Gender categorical<br>Units: Subjects              |                         |       |  |
| Female   | 4                       | 4     |  |
| Male   | 16                      | 16    |  |

### Subject analysis sets

|                            |   |
|----------------------------|---|
| Subject analysis set title | Pharmacodynamic analysis set Aspirin 20mg |
| Subject analysis set type  | Full analysis                             |

Subject analysis set description:

All patients randomised to receive study medication when receiving Aspirin 20mg

|                            |   |
|----------------------------|---|
| Subject analysis set title | Pharmacodynamic analysis set Aspirin 75mg |
| Subject analysis set type  | Full analysis                             |

Subject analysis set description:

All patients that received Aspirin 75mg

| Reporting group values                             | Pharmacodynamic analysis set Aspirin 20mg | Pharmacodynamic analysis set Aspirin 75mg |  |
|--|---|---|--|
| Number of subjects                                 | 20  | 20  |  |
| Age categorical<br>Units: Subjects                 |   |   |  |
| In utero   |   |   |  |
| Preterm newborn infants (gestational age < 37 wks) |   |   |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                |                |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation   | 64.3<br>± 11.9 | 64.3<br>± 11.9 |  |
| Gender categorical<br>Units: Subjects   |                |                |  |
| Female<br>Male  | 4<br>16        |                |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Sequence 1                                |
| Reporting group description:<br>Aspirin 20mg twice daily for 14 days and Ticagrelor 90mg twice daily for 14 days<br>Followed by Aspirin 75mg once daily for 14 days and Ticagrelor 90mg twice daily for 14 days |   |
| Reporting group title   | Sequence 2                                |
| Reporting group description:<br>Aspirin 75mg twice daily for 14 days and Ticagrelor 90mg twice daily for 14 days<br>Followed by Aspirin 20mg once daily for 14 days and Ticagrelor 90mg twice daily for 14 days |   |
| Subject analysis set title  | Pharmacodynamic analysis set Aspirin 20mg |
| Subject analysis set type   | Full analysis                             |
| Subject analysis set description:<br>All patients randomised to receive study medication when receiving Aspirin 20mg  |   |
| Subject analysis set title  | Pharmacodynamic analysis set Aspirin 75mg |
| Subject analysis set type   | Full analysis                             |
| Subject analysis set description:<br>All patients that received Aspirin 75mg  |   |

### Primary: Serum thromboxane

|  |                   |
|--|-------------------|
| End point title  | Serum thromboxane |
| End point description:   |                   |
| End point type   | Primary           |
| End point timeframe:<br>In steady state after 14 days of treatment after two hours following the last dose of the period |                   |

| End point values                     | Pharmacodynamic analysis set Aspirin 20mg | Pharmacodynamic analysis set Aspirin 75mg |  |  |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Subject analysis set                      | Subject analysis set                      |  |  |
| Number of subjects analysed          | 20  | 20  |  |  |
| Units: nanogram(s)                   |   |   |  |  |
| arithmetic mean (standard deviation) | 3.03 (± 3.64)                             | 0.83 (± 1.93)                             |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Overall analysis   |
| Statistical analysis description:<br>Post-dose serum TXB2 results for participants when receiving aspirin 20 mg twice daily vs. 75 mg once daily were analysed using a two-tailed paired t-test (3.03 ± 3.64 ng/ml vs. 0.83 ± 1.93 ng/ml, p=0.018). |  |
| Comparison groups   | Pharmacodynamic analysis set Aspirin 20mg v<br>Pharmacodynamic analysis set Aspirin 75mg |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 40                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | = 0.018                        |
| Method                                  | t-test, 2-sided                |
| Parameter estimate                      | Mean difference (final values) |

### Secondary: Bleeding time

|   |               |
|---|---------------|
| End point title   | Bleeding time |
| End point description:  |               |
| End point type  | Secondary     |
| End point timeframe:  |               |
| After each 14 day treatment period. Two hours after last dose |               |

| End point values                     | Pharmacodynamic analysis set Aspirin 20mg | Pharmacodynamic analysis set Aspirin 75mg |  |  |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Subject analysis set                      | Subject analysis set                      |  |  |
| Number of subjects analysed          | 20  | 20  |  |  |
| Units: second                        |   |   |  |  |
| arithmetic mean (standard deviation) | 679.5 (± 305.5)                           | 833.9 (± 385.7)                           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pre-dose serum thromboxane serum 2

|   |                                    |
|---|------------------------------------|
| End point title                                     | Pre-dose serum thromboxane serum 2 |
| End point description:                              |                                    |
| End point type                                      | Secondary                          |
| End point timeframe:                                |                                    |
| After 14 days of treatment and before the last dose |                                    |

| <b>End point values</b>              | Pharmacodynamic analysis set Aspirin 20mg | Pharmacodynamic analysis set Aspirin 75mg |  |  |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Subject analysis set                      | Subject analysis set                      |  |  |
| Number of subjects analysed          | 20  | 20  |  |  |
| Units: nanogram(s)                   |   |   |  |  |
| arithmetic mean (standard deviation) | 3.51 (± 4.07)                             | 2.48 (± 3.14)                             |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From enrollment to day 42 phone call

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Aspiring 20mg regime |
|-----------------------|----------------------|

Reporting group description: -

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Aspiring 75mg regime |
|-----------------------|----------------------|

Reporting group description: -

| Serious adverse events                            | Aspiring 20mg regime | Aspiring 75mg regime |  |
|---|----------------------|----------------------|--|
| Total subjects affected by serious adverse events |                      |                      |  |
| subjects affected / exposed                       | 0 / 20 (0.00%)       | 0 / 20 (0.00%)       |  |
| number of deaths (all causes)                     | 0                    | 0                    |  |
| number of deaths resulting from adverse events    | 0                    | 0                    |  |

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

| Non-serious adverse events                            | Aspiring 20mg regime | Aspiring 75mg regime |  |
|---|----------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                      |                      |  |
| subjects affected / exposed                           | 1 / 20 (5.00%)       | 4 / 20 (20.00%)      |  |
| General disorders and administration site conditions  |                      |                      |  |
| Epistaxis   |                      |                      |  |
| subjects affected / exposed                           | 0 / 20 (0.00%)       | 1 / 20 (5.00%)       |  |
| occurrences (all)                                     | 0                    | 1                    |  |
| Respiratory, thoracic and mediastinal disorders       |                      |                      |  |
| Respiratory tract infection                           |                      |                      |  |
| subjects affected / exposed                           | 0 / 20 (0.00%)       | 1 / 20 (5.00%)       |  |
| occurrences (all)                                     | 0                    | 1                    |  |
| Skin and subcutaneous tissue disorders                |                      |                      |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Haematoma                                       |                |                |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Oedema peripheral                               |                |                |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Chest discomfort                                |                |                |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 0 / 20 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported