



Clinical trial results:

A study of the effects of Simvastatin on neutrophil function in elderly subjects

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2011-002082-38 |
| Trial protocol | GB |
| Global end of trial date | 01 September 2013 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 27 November 2019 |
| First version publication date | 27 November 2019 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | RG_11-123 |
|-----------------------|-----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Edgbaston, Birmingham, United Kingdom, B15 2TT |
| Public contact | Clinical Trials Coordinator, Queen Elizabeth Hospital Birmingham NHS Trust, 44 01214721311, anita.pye@uhb.nhs.uk |
| Scientific contact | Clinical Trials Coordinator, Queen Elizabeth Hospital Birmingham NHS Trust, 44 01214721311, anita.pye@uhb.nhs.uk |
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Edgbaston, Birmingham, United Kingdom, B15 2TH |
| Public contact | Dr Elizabeth Sapey, University of Birmingham,, 44 1212462000, e.sapey@bham.ac.uk |
| Scientific contact | Dr Elizabeth Sapey, University of Birmingham,, 44 1212462000, e.sapey@bham.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 | 09 January 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 September 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Hypothesis. The age-related loss of neutrophil function contributes to delayed resolution of infection and inflammation. These changes in neutrophil function with advanced age are a result of alterations in signal transduction pathways due to altered membrane cholesterol levels and can be corrected using simvastatin. In vitro studies have confirmed that neutrophils isolated from elderly subjects respond differently to those from young donors in terms of migration, phagocytosis and superoxide production when pre-treated with physiological concentrations of Simvastatin. Question: Is this clinically relevant in vivo? Does a course of treatment with simvastatin improve migratory dynamics, phagocytosis and superoxide generation of neutrophils isolated from the peripheral blood of older subjects and is this associated with altered membrane cholesterol levels?

Protection of trial subjects:

As per EU and UK law with monitoring and safety checks as per the protocol

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 05 December 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: 24 |
| Worldwide total number of subjects | 24 |
| EEA total number of subjects | 24 |

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) | 3 |
| From 65 to 84 years | 12 |
| 85 years and over | 9 |

Subject disposition

Recruitment

Recruitment details:

24 participants were recruited but only 21 had the CTIMP or placebo, and 20 completed the full cross-over period. 20 were included in the analysis

Pre-assignment

Screening details:

Healthy old (OH) subjects, identified from among the Birmingham 1000 Elders cohort, had never smoked, had no evidence of acute or chronic disease, had normal spirometry, were medication free, and had no previous episodes of hospitalized sepsis.

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 24 |
| Number of subjects completed | 24 |

Period 1

| | |
|------------------------------|---|
| Period 1 title | Period 1 in cross over |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Study drugs (simvastatin or placebo) were prepared, randomised, and packaged identically by Bilcare Ltd (Powys, UK). Computer-based block randomisation was performed in a 1:1 ratio by a centralised service (Bilcare Ltd, UK) ready for period 2

Arms

| | |
|-----------|-------|
| Arm title | CTIMP |
|-----------|-------|

Arm description:

Simvastatin

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Simvastatin |
| Investigational medicinal product code | MA-PL0075/017 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

80mg once daily for 2 weeks

| Number of subjects in period 1 | CTIMP |
|--------------------------------|-------|
| Started | 24 |
| Completed | 20 |
| Not completed | 4 |
| Consent withdrawn by subject | 4 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Placebo cross over period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Study drugs (simvastatin or placebo) were prepared, randomised, and packaged identically by Bilcare Ltd (Powys, UK). Computer-based block randomisation was performed in a 1:1 ratio by a centralised service (Bilcare Ltd, UK)

Arms

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

Arm description:

Placebo in cross over

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | DBAAe capsule shells filled with Microcrystalline cellulose. |
| Investigational medicinal product code | MA-10284 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Once daily for 2 weeks

| | |
|---------------------------------------|---------|
| Number of subjects in period 2 | Placebo |
| Started | 20 |
| Completed | 20 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Period 1 in cross over |
|-----------------------|------------------------|

Reporting group description: -

| Reporting group values | Period 1 in cross over | Total | |
|---------------------------------------|------------------------|-------|--|
| Number of subjects | 24 | 24 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 3 | 3 | |
| From 65-84 years | 12 | 12 | |
| 85 years and over | 9 | 9 | |
| Gender categorical Units: Subjects | | | |
| Female | 15 | 15 | |
| Male | 9 | 9 | |

Subject analysis sets

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Baseline characteristics |
|----------------------------|--------------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

As this was a comparison of a change in neutrophil function, only those who completed the study were include din the analysis

| | |
|----------------------------|-------|
| Subject analysis set title | CTIMP |
|----------------------------|-------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

As this was a comparison of changes in neutrophil function, only those who completed the study were included

| | |
|----------------------------|---------|
| Subject analysis set title | Placebo |
|----------------------------|---------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

As this was a comparison of changes in neutrophil function, only those who completed the study were included

| Reporting group values | Baseline characteristics | CTIMP | Placebo |
|---------------------------------------|--------------------------|-------|---------|
| Number of subjects | 20 | 20 | 20 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 2 | 2 | 2 |
| From 65-84 years | 10 | 10 | 10 |
| 85 years and over | 8 | 8 | 8 |
| Gender categorical Units: Subjects | | | |
| Female | 11 | 11 | 11 |
| Male | 9 | 9 | 9 |

End points

End points reporting groups

| | |
|--|--------------------------|
| Reporting group title | CTIMP |
| Reporting group description: Simvastatin | |
| Reporting group title | Placebo |
| Reporting group description: Placebo in cross over | |
| Subject analysis set title | Baseline characteristics |
| Subject analysis set type | Per protocol |
| Subject analysis set description: As this was a comparison of a change in neutrophil function, only those who completed the study were include din the analysis | |
| Subject analysis set title | CTIMP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: As this was a comparison of changes in neutrophil function, only those who completed the study were included | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Per protocol |
| Subject analysis set description: As this was a comparison of changes in neutrophil function, only those who completed the study were included | |

Primary: Median change in neutrophil migration to fMLP

| | |
|--|---|
| End point title | Median change in neutrophil migration to fMLP |
| End point description: | |
| End point type | Primary |
| End point timeframe: After 2 weeks of CTIMP therapy | |

| End point values | CTIMP | Placebo | | |
|---------------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: um/min | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.34 (0.05 to 0.72) | -0.05 (-0.38 to 0.08) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Change in chemotaxis from baseline values |
| Comparison groups | CTIMP v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Change in chemotaxis towards CXCL8

| | |
|---|------------------------------------|
| End point title | Change in chemotaxis towards CXCL8 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Compared to baseline after 2 weeks of therapy in cross over trial | |

| End point values | CTIMP | Placebo | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: um/min | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.26 (0.01 to 0.61) | 0.03 (-0.73 to 0.34) | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | Change from baseline chemotaxis |
| Comparison groups | CTIMP v Placebo |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.042 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Change in phagocytosis E Coli

| | |
|---|-------------------------------|
| End point title | Change in phagocytosis E Coli |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| After two weeks of CTIMP or placebo in cross over trial | |

| End point values | CTIMP | Placebo | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: arbitrary units | | | | |
| median (inter-quartile range (Q1-Q3)) | 580 (-22.0 to 1347) | 690 (-79.0 to 1207) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Change in phagocytosis E Coli |
| Comparison groups | CTIMP v Placebo |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.404 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Change in phagocytosis staph aureus

| | |
|---|-------------------------------------|
| End point title | Change in phagocytosis staph aureus |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| After 2 weeks of CTIMP or placebo in cross over trial | |

| End point values | CTIMP | Placebo | | |
|---------------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: arbitrary units | | | | |
| median (inter-quartile range (Q1-Q3)) | 257 (-616.7 to 1951) | 1217 (-588.7 to 2048) | | |

Statistical analyses

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Change in phagocytic index |
| Comparison groups | CTIMP v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.196 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: NETosis PMA

| | |
|---|-------------|
| End point title | NETosis PMA |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Two weeks of CTIMP or placebo in cross over study | |

| End point values | CTIMP | Placebo | | |
|---------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Arbitrary Units | | | | |
| median (inter-quartile range (Q1-Q3)) | 5985 (-24415 to 30189) | 6964 (-17992 to 22048) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Change in PMA induced NETs |
| Comparison groups | CTIMP v Placebo |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 729 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: NETosis to fMLP

| | |
|-------------------------------------|-----------------|
| End point title | NETosis to fMLP |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| After two weeks of CTIMP or Placebo | |

| End point values | CTIMP | Placebo | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Arbitrary Units | | | | |
| median (inter-quartile range (Q1-Q3)) | 1355 (-2133 to 6518) | 1099 (-2818 to 2719) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Change in ketosis to fMLP |
| Comparison groups | CTIMP v Placebo |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.216 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Netosis to LPS

| | |
|---|----------------|
| End point title | Netosis to LPS |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| After 2 weeks of CTIMP or placebo in cross over trial | |

| End point values | CTIMP | Placebo | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Arbitrary Units | | | | |
| median (inter-quartile range (Q1-Q3)) | 7115 (-839 to 9851) | 4048 (2833 to 6279) | | |

Statistical analyses

| | |
|-----------------------------------|--------------------------|
| Statistical analysis title | Change in Netosis to LPS |
| Comparison groups | CTIMP v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.596 |
| Method | Wilcoxon (Mann-Whitney) |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For up to two weeks after completion of study

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

Dictionary used

| | |
|-----------------|-----|
| Dictionary name | ICD |
|-----------------|-----|

| | |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | All subjects |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events | All subjects | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | All subjects | | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle ache | Additional description: Muscle ache in one subject with no change in blood tests and able to complete study | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 04 May 2012 | Justification in protocol for giving 80mg Simvastatin, as requested by MHRA |

Notes:

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/28657793>