



Clinical trial results:

A randomised, double-blind, placebo-controlled trial of metformin in chronic obstructive pulmonary disease (COPD) exacerbations: a pilot study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-020818-28 |
| Trial protocol | GB |
| Global end of trial date | 10 April 2014 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 13 November 2019 |
| First version publication date | 13 November 2019 |
| Summary attachment (see zip file) | Thorax Article (Thorax 2016 - Metformin in COPD trial.pdf) End of Trial Report (Metformin End of Study Report draft 1.0.doc) |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 10.0086 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | St Georges University of London |
| Sponsor organisation address | Cranmer Terrace, London, United Kingdom, SW17 0RE |
| Public contact | Joint Research Office, sponsor@sgul.ac.uk, Prof Emma Baker ebaker@sgul.ac.uk, 0208725501 02087255012, sponsor@sgul.ac.uk |
| Scientific contact | Joint Research Office, sponsor@sgul.ac.uk, Prof Emma Baker ebaker@sgul.ac.uk, 0208725501 02087255012, ebaker@sgul.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 | 01 February 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 March 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 April 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The overarching research question for this body of work is to ascertain whether metformin improves recovery from COPD exacerbations.

This pilot study will address a more limited question, as a basis for future trial design: in patients admitted to hospital with COPD exacerbations, is metformin an effective treatment for acute hyperglycaemia (elevated blood sugar concentration)?

Protection of trial subjects:

This trial will be monitored on a daytoday basis by the study team. Oversight will be provided by the steering committee, chaired by the chief investigator. A patient representative, and a researcher from outside the trial group, shall be invited to attend steering group meetings. No interim data analyses are planned

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 19 January 2011 |
| 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: 52 |
| Worldwide total number of subjects | 52 |
| EEA total number of subjects | 52 |

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) | 52 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment within UK only.

Pre-assignment

Screening details:

Baseline measurements will then be taken. This will include a validated 8item questionnaire to quantify the impact

that COPD is having on the patients' wellbeing and daily life (the COPD Assessment Test, CAT) and blood tests. Once daily

measurement of symptoms will be commenced (using the a 14item validated tool, the Exacerbations of Chronic

Pu

Period 1

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

Blinding implementation details:

A double-blinded design has been adopted to provide the best possible evidence for the efficacy of metformin in this context by minimising the risk of bias. Blinding will be implemented by means of visually identical active and placebo treatments. Randomisation lists will be produced in advance by the drug manufacturer and will be provided to the sponsor / lead site Pharmacy department for the purposes of allocation and/or emergency unblinding

Arms

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

Arm description:

active

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

Dosage and administration details:

2000 mg Capsule

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

Arm description: -

| | |
|--|------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Buccal use |

Dosage and administration details:

500mg oral

| Number of subjects in period 1 | active | Placebo |
|---------------------------------------|--------|---------|
| Started | 34 | 18 |
| Completed | 34 | 18 |

Baseline characteristics

End points

End points reporting groups

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

Primary: Primary

| | |
|---|---------|
| End point title | Primary |
| End point description: | |
| End point type | Primary |
| End point timeframe: Mean capillary glucose concentration during hospitalisation period—defined as the mean of all capillary glucose measurements obtained according to the study protocol for that patient during the period between enrolment in the trial and hospital discharge. | |

| End point values | active | Placebo | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 18 | | |
| Units: 00 | | | | |
| arithmetic mean (full range (min-max)) | 00 (00 to 00) | 00 (00 to 00) | | |

Statistical analyses

| | |
|---|-------------------|
| Statistical analysis title | Primary End-Point |
| Comparison groups | Placebo v active |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.273 |
| Method | Not known |

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Within 24 hours to the sponsor and CI from becoming aware

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

Dictionary used

| | |
|-----------------|------|
| Dictionary name | SmPC |
|-----------------|------|

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

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: All Adverse Event data can be viewed in the End of Trial Report.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 30 November 2010 | <p>Substantial amendment 1</p> <ul style="list-style-type: none"> - Changes made in relation to conditions specified by the REC in the REC approval letter dated 16th September 2010. - Additional site at Chelsea & Westminster Hospital added - The definition of severe sepsis as an exclusion criterion and as a treatment suspension criterion has been modified. - Changes have been made to the randomisation procedure and emergency unblinding in the protocol - Additional study assessments have been included: <ul style="list-style-type: none"> Monocyte-platelet aggregates Bacterial metagenomic analysis from a buccal (mouth) swab sample |
| 19 January 2011 | <p>Substantial amendment 2 19 January 2011</p> <ul style="list-style-type: none"> - Minor changes made to the simplified IMPD to remove reference to the study protocol. This is to avoid having to amend the sIMPD every time we amend the study protocol and consequently change its version number. - Randomisation amended in protocol to blocks of 4 for C&W and blocks of 6 for SGUL - Pharmacovigilance section amended regarding wording and reporting requirements |
| 22 August 2011 | <p>Substantial amendment 3 22 August 2011</p> <p>Substantial Amendment 3 first submitted to REC and MHRA on 22 August 2011 with the following major changes:</p> <ol style="list-style-type: none"> Inclusion/exclusion criteria amended: <ol style="list-style-type: none"> Inclusion criterion 4 (able to enter the study within 48 hours of admission) has been amended as the study team have found this criterion quite restrictive, precluding study entry for a significant proportion of patients screened. The definition of exclusion criterion 4 (acute coronary syndrome), has been updated to accommodate the introduction of fondaparinux in place of dalteparin in the treatment of this condition. The 'monocyte-platelet aggregates' assessment has been removed as it was not possible to establish the necessary laboratory assay. The upper limit for the acceptable plasma lactate concentration has been increased from 2.7 to 3.0 mmol/L. The requirement that study therapy be stopped pre-emptively in patients requiring a radiological examination with the administration of intravenous contrast has been removed Addition of 4 new sites – Conquest Hospital, Hastings, Freeman Hospital, Nottingham, North Tees and New Castle We would like to extend the study end date to 31st December 2012. Change of PI at St George's from Dr Andrew Hitchings to Professor Emma Baker <p>MHRA rejected first submission on 26/09/2011 with GNA. Resubmitted to MHRA on 04th October 2011 & REC on 06th October 2011 with further change in protocol to include the foll: "Retention of a requirement to suspend metformin before administration of intravascular iodinated contrast agent and that it not be reinstituted until 48 hours afterwards and only after renal functions has been re-evaluated and found to be normal' as per SmPC."</p> |

| | |
|---------------|---|
| 29 June 2012 | <p>Substantial amendment 4 29th June 2012</p> <ol style="list-style-type: none"> 1. The active: placebo allocation ratio will increase from 1:1 to 2:1. Accordingly, the target sample size will increase from 46 to 69 participants.. 2. To accommodate 2:1 allocation, the randomisation block size will be fixed at 6. 3. The intention to explore feasibility, safety and tolerability of the investigational treatment will be made explicit. 4. The secondary exploratory endpoints based on collection of a buccal swab and performance of the McKenzie skin blanch test will be removed, as it has not proved feasible to perform these tests with sufficient reliability. 5. The number of missed capillary glucose concentration measurements (≥ 3 out of 7 in a calendar day), or the maximum interval between consecutive measurements (>12 h), that will constitute a protocol deviation shall be defined. 6. Recurrence of COPD exacerbation will be added as a Protocol Defined Event, as it is a common event in the population under study, and contributes to the secondary analysis. 7. Change of sponsor contact from Ira Jakupovic (Clinical R&D Manager) to Nicki Collins (Sponsor representative). <p>The Participant Information Leaflet, Informed Consent Form and GP Letter have been updated due to the changes in the protocol and also submitted for your review in tracked and clean versions.</p> |
| 03 April 2013 | <p>Substantial amendment 5 03rd April 2013</p> <ul style="list-style-type: none"> • 1. Adding new sites in uk • 2. Extending the recruitment period <ol style="list-style-type: none"> 3. A typographical error has been correct in the introductory section 4. Definitions for 'expectedness' have been updated to align with standard regulatory framework 5. The interpretation of Protocol Defined Events has been clarified 6. Fructosamine concentration has been added as a secondary endpoint 7. The terms used for sampling time-points have been standardised within the protocol 8. Reference to a Trial Management Group has been removed, as in practice, its membership and function has become the same as that of the Trial Steering Committee • 9. Updating GP letter in light of these changes • 10. Change of sponsor representative to Lucy Parker |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported