



## Clinical trial results:

### A single arm double-blind placebo controlled cross-over trial of Aprepitant for the treatment of cough in lung cancer: "CALC" Trial

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2013-000139-28   |
| Trial protocol           | GB               |
| Global end of trial date | 17 November 2014 |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 21 June 2019   |
| First version publication date    | 21 June 2019   |
| Summary attachment (see zip file) | Final Study Report (CALC trial Final Study Report 12 May 2015.pdf)<br>Abstract (CALC ASCO abstract 2015.pdf) |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | 12_DOG07_146 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN16200035 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | The Christie NHS Foundation Trust   |
| Sponsor organisation address | Wilmslow Road, Manchester, United Kingdom, M20 4BX  |
| Public contact               | Christiesponsoredresearch, The Christie NHS Foundation Trust,<br>0044 01619187357,<br>Christiesponsoredresearch@christie.nhs.uk |
| Scientific contact           | Christiesponsoredresearch, The Christie NHS Foundation Trust,<br>0044 01619187357,<br>Christiesponsoredresearch@christie.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:

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## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 12 May 2015      |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 17 November 2014 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 17 November 2014 |
| Was the trial ended prematurely?                     | No               |

Notes:

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## General information about the trial

Main objective of the trial:

Primary)

To demonstrate that aprepitant significantly reduces objective cough rates (frequency) over placebo.

Secondary)

To determine the effect of aprepitant on cough-specific quality of life (MCLCS) scores for LC participants.

To determine the effect of aprepitant on Visual Analogue Scale (VAS) scores for LC participants.

To determine whether Gastro-oesophageal reflux disease (GORD) and nausea correlate with cough severity and treatment response.

To determine whether Global QoL is affected by cough severity

To estimate the minimum important difference (MID) for the Manchester Cough in Lung Cancer Scale.

To determine whether biomarkers can predict cough severity.

To determine whether aprepitant should be tested in a larger definitive study.

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Protection of trial subjects:

Participation:

In order to minimise the impact of participation in this study, we are conducting a short study with no follow up beyond 9 days. We will recruit patients with a good performance status (02). Patient participation is voluntary and patients can withdraw from the study at any time.

Treatment:

Aprepitant is already licensed for the treatment of chemotherapy induced nausea. It is widely used in Oncology and is extremely well tolerated by patients. As Aprepitant is not licensed for treatment of cough, patients will be withdrawn from the study if they develop significant toxicities.

Questionnaires:

The Manchester Cough in Lung Cancer Scale is a 10item questionnaire which takes 23 minutes to complete. There are no sensitive items. The Visual Analogue Scale (VAS)takes less than a minute to complete to show how severe the patient feels their cough is. 178 patients in a previous study that we conducted(Cough in Lung Cancer: CLiC Study) have not reported any ethical difficulties filling in these questionnaires

Blood samples:

Patients may have some pain and bruising relating to the taking of 2 blood samples. Where possible, the trial blood tests will be taken at the same time as routine blood samples for their standard oncology care to minimise burden.

Ambulatory cough monitoring with 24 hour recordings:

A full 24hour recording is necessary since cough may vary significantly during the day and night. Should a patient feel too unwell to return the cough monitors to the hospital, where possible, the study investigator will collect the cough monitor from the patient's home address.All recordings will be anonymised. The study investigator will be analysing the number of coughs and time spent coughing, disregarding all other content of the recordings. SOPs are in place at the North West Lung Centre which the study investigator will adhere to

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Background therapy: -

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Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 01 April 2013 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

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

Notes:

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#### Subjects enrolled per age group

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|   |    |
|---|----|
| 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:

Participants were recruited from the medical and clinical oncology follow-up clinics at The Christie. The source population consists of all participants who attend specific, identified outpatient clinics after the recruitment start date.

### Pre-assignment

Screening details:

Prior to trial recruitment, participants need to have had LFTs measured within the 2-week period prior to trial entry. The LFTs need to be no more than 1.5x ULN except for bilirubin which needs to be within normal limits according to The Christie NHS Foundation pathology laboratory.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall Trial (overall period)                                |
| 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:

A randomisation list was generated by the MAHSC CTU containing:

- the participant ID number
- a random sequence of drug i.e. aprepitant followed by placebo or placebo followed by aprepitant

This list was supplied to the clinical trials pharmacy team at The Christie NHS Foundation Trust to dispense the blinded medication upon receipt of a prescription stating the participant's randomisation number and label the aprepitant or placebo to ensure the blind is maintained.

### Arms

|           |            |
|-----------|------------|
| Arm title | Cross-Over |
|-----------|------------|

Arm description:

Cross-over arm Aprepitant / Placebo

|  |            |
|--|------------|
| Arm type                               | Cross-Over |
| Investigational medicinal product name | Aprepitant |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Capsule    |
| Routes of administration               | Oral use   |

Dosage and administration details:

Participants will receive aprepitant/placebo capsules 125mg on Day 1, followed by aprepitant/placebo capsules 80mg on Day 2 and Day 3. There will then be a 3 day wash-out period followed by aprepitant/placebo capsules 125mg on Day 7, followed by aprepitant/placebo capsules 80mg on Day 8 and Day 9

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

Dosage and administration details:

Participants will receive aprepitant/placebo capsules 125mg on Day 1, followed by aprepitant/placebo capsules 80mg on Day 2 and Day 3. There will then be a 3 day wash-out period followed by aprepitant/placebo capsules 125mg on Day 7, followed by aprepitant/placebo capsules 80mg on Day 8 and Day 9

| <b>Number of subjects in period 1</b> | Cross-Over |
|---------------------------------------|------------|
| Started                               | 20         |
| Completed                             | 19         |
| Not completed                         | 1          |
| Adverse event, non-fatal              | 1          |

## Baseline characteristics

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### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Trial | Total |  |
|------------------------|---------------|-------|--|
| Number of subjects     | 20            | 20    |  |
| Age categorical        |               |       |  |
| Units: Subjects        |               |       |  |
| Adults (18-64 years)   | 10            | 10    |  |
| From 65-84 years       | 10            | 10    |  |
| 85 years and over      | 0             | 0     |  |
| Gender categorical     |               |       |  |
| Units: Subjects        |               |       |  |
| Female                 | 12            | 12    |  |
| Male                   | 8             | 8     |  |

## End points

### End points reporting groups

|                                     |            |
|-------------------------------------|------------|
| Reporting group title               | Cross-Over |
| Reporting group description:        |            |
| Cross-over arm Aprepitant / Placebo |            |

### Primary: Cough Monitoring - baseline frequency

|                 |  |
|-----------------|--|
| End point title | Cough Monitoring - baseline frequency <sup>[1]</sup> |
|-----------------|--|

End point description:

Objective cough monitoring was conducted in 20 patients at baseline (day 0), but 1 patient was excluded as they commenced treatment at baseline rather than day 1. Of these, no recordings failed.

The baseline geometric mean cough frequency over 24 hours was 13.3 coughs/hour with a 95%CI of 8.2-21.6 (n=19)

The daytime (defined as hours patient awake) cough frequency was 15.9 coughs/hour with a 95%CI of 10.1-28.3 (n=19)

The night-time (defined as patient hours asleep) the median cough frequency was 5.9 coughs/hour with a 25th-75th IQR of 1.9-10.7 with a total range of 0-17.45 (n=19)

Within the trial population, a subset of patients responded to aprepitant and showed improvement in both subjective and objective cough scores. However, other patients showed no improvement. The baseline day-time cough frequency did not predict or influence the response to treatment (p=0.17).

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Patients underwent 24 hour ambulatory cough monitoring on days 0, 3 and 9 of the trial duration.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was performed in accordance with the protocol.

| End point values                         | Cross-Over         |  |  |  |
|--|--------------------|--|--|--|
| Subject group type                       | Reporting group    |  |  |  |
| Number of subjects analysed              | 19 <sup>[2]</sup>  |  |  |  |
| Units: 13.3 coughs/hour                  |                    |  |  |  |
| geometric mean (confidence interval 95%) | 13.3 (8.2 to 21.6) |  |  |  |

Notes:

[2] - one patient excluded since they commence treatment at baseline (day 0) rather than day 1

### Statistical analyses

No statistical analyses for this end point

### Primary: Cough Monitoring - Day time (Aprepitant)

|                 |   |
|-----------------|---|
| End point title | Cough Monitoring - Day time (Aprepitant) <sup>[3]</sup> |
|-----------------|---|

End point description:

1There was high compliance with the study schedule, with only one patient failing to complete the trial protocol due to chest infection. One patient was excluded due to commencing treatment on day 0, rather than day 1.

Daytime cough frequency = 12.8 (95% CI 8.7-18.8 n=18) on aprepitant.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Cough monitoring was collected at day 0, 3 and 9 during the trial duration.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was performed in accordance with the protocol.

|  |                    |  |  |  |
|--|--------------------|--|--|--|
| <b>End point values</b>                  | Cross-Over         |  |  |  |
| Subject group type                       | Reporting group    |  |  |  |
| Number of subjects analysed              | 18 <sup>[4]</sup>  |  |  |  |
| Units: 12.8 coughs/hour                  |                    |  |  |  |
| geometric mean (confidence interval 95%) | 12.8 (8.7 to 18.8) |  |  |  |

Notes:

[4] - 1 patient failed to complete protocol, 1 patient was excluded.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cough Monitoring - Day time (Placebo)

|                 |  |
|-----------------|--|
| End point title | Cough Monitoring - Day time (Placebo) <sup>[5]</sup> |
|-----------------|--|

End point description:

Daytime cough frequency was 15.9 (95%CI 10.1-28.3 n=19), 12.8 (95% CI 8.7-18.8 n=18) and 16.2 (11.3-23.0 n=19) coughs/hr at baseline, on aprepitant and on placebo respectively: p=0.03.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Cough monitoring was conducted on day 0, 3 and 9 of the trial duration

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was performed in accordance with the protocol.

|  |                     |  |  |  |
|--|---------------------|--|--|--|
| <b>End point values</b>                  | Cross-Over          |  |  |  |
| Subject group type                       | Reporting group     |  |  |  |
| Number of subjects analysed              | 19 <sup>[6]</sup>   |  |  |  |
| Units: 16.2 coughs/hour                  |                     |  |  |  |
| geometric mean (confidence interval 95%) | 16.2 (11.3 to 23.0) |  |  |  |

Notes:

[6] - one patient excluded.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Cough Severity VAS

|                 |                    |
|-----------------|--------------------|
| End point title | Cough Severity VAS |
|-----------------|--------------------|

End point description:

The median cough severity VAS score was 59mm (25th - 75th IQR 37-66), score range 0-100 where higher scores represent worse cough severity.



Visual analogue scale scores (range 0-100, high score=worse severity) were  
 Baseline: 57.0mm (95% CI 47.4-67.2 n=19),  
 Aprepitant: 40.8mm, (95%CI 34.3-47.3 n=18),  
 Placebo: 49.8mm (95%CI 44.2-55.4 n=19); p=0.008.

Overall, 8 (40%) patients reported an improvement from baseline by one point in cough severity on aprepitant compared to 5 (25%) patients reporting an improvement on placebo from baseline.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| VAS questionnaires were conducted on days 0, 3 and 9 of the trial period. |           |

|                                       |                   |  |  |  |
|---------------------------------------|-------------------|--|--|--|
| <b>End point values</b>               | Cross-Over        |  |  |  |
| Subject group type                    | Reporting group   |  |  |  |
| Number of subjects analysed           | 19 <sup>[7]</sup> |  |  |  |
| Units: 59                             |                   |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 59 (37 to 66)     |  |  |  |

Notes:

[7] - one patient failed to complete trial protocol due to chest infection.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Manchester Cough in Lung Cancer Scale (MCLCS)

|                 |   |
|-----------------|---|
| End point title | Manchester Cough in Lung Cancer Scale (MCLCS) |
|-----------------|---|

End point description:

The median MCLCS was about half of the total score range at 25.5 (25th - 75th IQR 20-31), range 1-50 where higher scores represent worse cough impact.

The Manchester Cough in Lung Cancer Scale score was:

Baseline: 25.2 (95%CI 23.0-28.0 n=19),  
 Aprepitant: 19.5 (95%CI 17.8-21.2 n=18)  
 Placebo: 21.7 (20.3-23.1 n=18) p<0.001

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| MCLCS were collected at days 0, 3 and 9 of the trial period. |           |

|                                       |                   |  |  |  |
|---------------------------------------|-------------------|--|--|--|
| <b>End point values</b>               | Cross-Over        |  |  |  |
| Subject group type                    | Reporting group   |  |  |  |
| Number of subjects analysed           | 19 <sup>[8]</sup> |  |  |  |
| Units: 25.5                           |                   |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 25.5 (20 to 31)   |  |  |  |

Notes:

[8] - One patient failed to complete trial protocol due to chest infection

## Statistical analyses

No statistical analyses for this end point

### Secondary: EORTC - LC 13

|                 |               |
|-----------------|---------------|
| End point title | EORTC - LC 13 |
|-----------------|---------------|

End point description:

The mean EORTC LC 13 item 31 score was 61.6 (SD 19.6), where higher scores indicate a worse cough severity on a scale of 0-100.

There was little change in the overall score for individual patients during treatment with placebo and aprepitant. The EORTC QLQ LC13 cough item only varied by one point for individual patients.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

EORTC questionnaires were collected on days 0, 3 and 9 of the trial period

| End point values                     | Cross-Over        |  |  |  |
|--------------------------------------|-------------------|--|--|--|
| Subject group type                   | Reporting group   |  |  |  |
| Number of subjects analysed          | 19 <sup>[9]</sup> |  |  |  |
| Units: 61.6                          |                   |  |  |  |
| arithmetic mean (standard deviation) | 61.6 (± 19.6)     |  |  |  |

Notes:

[9] - one patient failed to complete trial protocol

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Duration of study including telephone follow-up on day 13 or 14

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Cross-Over |
|-----------------------|------------|

Reporting group description:

Cross-over arm Aprepitant / Placebo

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

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

| Non-serious adverse events                            | Cross-Over     |  |  |
|---|----------------|--|--|
| Total subjects affected by non-serious adverse events |                |  |  |
| subjects affected / exposed                           | 1 / 20 (5.00%) |  |  |
| Respiratory, thoracic and mediastinal disorders       |                |  |  |
| Chest Infection                                       |                |  |  |
| subjects affected / exposed                           | 1 / 20 (5.00%) |  |  |
| occurrences (all)                                     | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 23 July 2013    | SA02 - Change to IMPD documentation to document change in IMP containers to include desiccant.  |
| 03 October 2013 | SA03 - Protocol v4.0 (09/09/2013). Change to exclusion criteria. Change to PIS to clearly state that if patients withdraw and do not wish for research to use their data, that their blood samples will be destroyed. |
| 10 October 2013 | SA1 - Addition of Global Rating of Change Scale (GRCS) to the protocol v3.0 (25.03.13). Update of PIS/ICF/GP letter v4.0 (25.03.13)   |
| 25 June 2014    | SA04 - Temporary Halt to recruitment. Protocol v5.0, PIS v6.0 - submitted to rectify a discrepancy relating to blood sampling between the trial protocol & the approved version of the patient information sheet.     |
| 27 June 2014    | SA05 - SA to inform the MHRA of an extension to the shelf life of IMP (from 15/02/2014 to 15/05/2014) and then from (15/05/2014 to 30/11/2014).   |
| 17 July 2014    | SA06 - Re-opening of study following temporary halt on the 15/05/2014 after the protocol and PIS discrepancy was resolved and approved by REC.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date        | Interruption   | Restart date |
|-------------|--|--------------|
| 15 May 2014 | Temporary Halt to recruitment following identification of a discrepancy between the trial protocol & the approved version of the patient information sheet in which day 0 blood collections were not specified in the PIS. Approached REC to clarify the use of a baseline blood sample for the patients already enrolled and to ensure that the patient information sheet is amended prior to any further patients being recruited. | 17 July 2014 |

Notes:

### Limitations and caveats

None reported