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) 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, 0044 01619187357, Christiesponsoredresearch@christie.nhs.uk
Scientific contact	Christiesponsoredresearch, The Christie NHS Foundation Trust, 0044 01619187357, 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:

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:

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.

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

Background therapy: -

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:

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:

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

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

Baseline characteristics

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 - basline frequency

End point title	Cough Monitoring - basline frequency[1]

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 then 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[2]			
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 then 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)[3]

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 then 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.

End point values	Cross-Over			
Subject group type	Reporting group			
Number of subjects analysed	18[4]			
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)[5]

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.

End point values	Cross-Over			
Subject group type	Reporting group			
Number of subjects analysed	19[6]			
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.

End point values	Cross-Over			
Subject group type	Reporting group			
Number of subjects analysed	19[7]			
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.

End point values	Cross-Over			
Subject group type	Reporting group			
Number of subjects analysed	19[8]			
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[9]			
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 no 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 15/02/20174 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