



## Clinical trial results:

**A single-centre, double-blind, randomised, placebo-controlled crossover study to evaluate the effect of solithromycin on airway inflammation in male and female patients with chronic obstructive pulmonary disease.**

### Summary

EudraCT number	2014-003077-42
Trial protocol	GB
Global end of trial date	05 January 2017

### Results information

Result version number	v1 (current)
This version publication date	09 February 2018
First version publication date	09 February 2018
Summary attachment (see zip file)	Final report (CE01-204 Study Report Body (ID 154418).pdf)

### Trial information

#### Trial identification

Sponsor protocol code	CE01-204
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02628769
WHO universal trial number (UTN)	-
Other trial identifiers	REC number: 14/LO/2066

Notes:

#### Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	AHSC Joint Research Compliance Office 510B, Charing Cross Hospital, Fulham Palace Road, London, United Kingdom, W6 8RF
Public contact	Louise Donnelly, Imperial College London, 44 02075947895,
Scientific contact	Louise Donnelly, Imperial College London, 44 02075947895, l.donnelly@imperial.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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 November 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 January 2017
Was the trial ended prematurely?	Yes

Notes:

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## General information about the trial

Main objective of the trial:

The main objective was to assess the effect, at day 28, of oral Solithromycin (CEM-101) on the number of sputum neutrophils per mL in subjects with chronic obstructive pulmonary disease (COPD) compared to placebo.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP).

Each subject was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and it was ensured that the Informed Consent Form was signed and dated before any study specific procedure was performed. Opportunity was given to ask questions and subjects were allowed time to consider the information provided. Subjects were also notified that they were free to discontinue from the study at any time. Written informed consent was obtained from all subjects prior to initiation of the study. Trial subjects were monitored at baseline and weekly throughout the study by the study doctor.

Background therapy:

Relevant treatment [prior/current medications, including all prescription/non-prescription medications, herbal medications, and vitamin supplements, and prior/current non-pharmacological (surgery, procedures) treatments] received by the subject within 7 days before administration of study drug were recorded. All enrolled subjects were receiving long acting combination corticosteroid and  $\beta$ 2-agonist inhaled preparations and 5 subjects received tiotropium bromide, a long-acting inhaled anticholinergic bronchodilator, for treatment of COPD. In addition to these treatments, 5 subjects received salbutamol, a short-acting  $\beta$ 2-agonist inhaler, for rescue therapy. Other concomitant medications used by at least 2 subjects included omeprazole (n=3) and statins (n=2).

Evidence for comparator:

Solithromycin (CEM-101) is a novel macrolide and the first fluoroketolide. It is active against Gram-positive, Gram-negative and atypical bacteria and is in clinical development for the treatment of community-acquired bacterial pneumonia and gonorrhoea. Development of solithromycin resistance has not been observed to date in clinical trials and solithromycin is active against bacterial strains that are resistant to other macrolides. It is 8-16 times more active than azithromycin and has a one day duration of action.

In a small clinical Phase 1 study, oral solithromycin (400 mg) once daily was substantially concentrated in lung epithelial lining fluid (~10-fold) and alveolar macrophages (~200-fold) compared to plasma concentrations, indicating its suitability for local effects in the lung. Solithromycin was found to have greater anti-inflammatory effects than other macrolides, such as erythromycin, azithromycin, clarithromycin and telithromycin (10-fold greater effect) in suppressing TNF- $\alpha$ , CXCL8 and MMP-9 release and activity from a human macrophage cell line and from monocytes from COPD patients. In addition solithromycin completely inhibited oxidative stress-activated NF- $\kappa$ B in these cells. Furthermore, solithromycin was effective in suppressing corticosteroid resistance indicating that, as well as a direct anti-inflammatory effect through NF- $\kappa$ B inhibition, it may also reverse corticosteroid resistance in COPD.

Actual start date of recruitment	01 December 2014
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: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	0
From 65 to 84 years	6
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment started 1st December 2014 in the UK with the first screening visit 29th September 2015  
Trial was terminated early 18th January 2017

### Pre-assignment

Screening details:

Screening procedures to determine subject eligibility were performed with 21 days to the first dose administration

### Pre-assignment period milestones

Number of subjects started	6
Number of subjects completed	6

### Period 1

Period 1 title	Overall study (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:

Participants were randomly assigned in a 1:1 ratio to receive either Solithromycin (400mcg) orally once a day for 28 days or matching placebo. Participants who were randomized to Solithromycin initially then received placebo for 28 days after a 28 day wash out period and vice versa.

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Solithromycin

Arm description:

Subjects received 400 mcg Solithromycin for 28 days and then matching placebo for an additional period of 28 days following a washout period of 28 days between the two treatments.

Arm type	Experimental
Investigational medicinal product name	Solithromycin
Investigational medicinal product code	CEM-101
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

400 mcg taken orally as 2X200 mcg capsules of Solithromycin once a day for 28 days

<b>Arm title</b>	Placebo
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Arm description:

Matching placebo was administered orally as capsules once a day for 28 days

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsule was taken once a day orally for 28 days

<b>Number of subjects in period 1</b>	Solithromycin	Placebo
Started	6	6
Completed	3	4
Not completed	3	2
Physician decision	-	1
Termination of trial	-	1
Adverse event, non-fatal	3	-

## Baseline characteristics

### Reporting groups

Reporting group title	Overall study (overall period)
Reporting group description:	
All subjects	

Reporting group values	Overall study (overall period)	Total	
Number of subjects	6	6	
Age categorical			
Units: Subjects			
From 65-84 years	6	6	
Age continuous			
Age of participants at the start of the trial			
Units: years			
arithmetic mean	69.3		
standard deviation	± 3.6	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	3	3	
Weight			
Units: kg			
arithmetic mean	75.2		
standard deviation	± 7.7	-	
Height			
Units: cm			
arithmetic mean	168.2		
standard deviation	± 3.4	-	
BMI			
Units: kg/m2			
arithmetic mean	26.7		
standard deviation	± 3	-	
Smoking history			
Units: pack years			
arithmetic mean	31.5		
standard deviation	± 10.0	-	
FEV1			
Lung function parameter			
Units: litre(s)			
arithmetic mean	1.29		
standard deviation	± 0.03	-	
FEV1 % predicted			
Units: percent			
arithmetic mean	55.2		
standard deviation	± 17.4	-	
FVC			
Units: litre(s)			

arithmetic mean	2.87		
standard deviation	± 0.81	-	
FEV1/FVC			
Units: ratio			
arithmetic mean	0.48		
standard deviation	± 0.14	-	
R5-R20			
Small airway function measurement			
Units: kPa.L-1.s			
arithmetic mean	0.18		
standard deviation	± 0.12	-	
CAT Score			
Units: Score			
arithmetic mean	17		
standard deviation	± 7.3	-	

## End points

### End points reporting groups

Reporting group title	Solithromycin
Reporting group description: Subjects received 400 mcg Solithromycin for 28 days and then matching placebo for an additional period of 28 days following a washout period of 28 days between the two treatments.	
Reporting group title	Placebo
Reporting group description: Matching placebo was administered orally as capsules once a day for 28 days	

### Primary: Sputum neutrophil counts

End point title	Sputum neutrophil counts <sup>[1]</sup>
End point description:	

End point type	Primary
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End point timeframe:

Measurement of sputum neutrophils after drug or placebo

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: Due to early termination of the study, there were too few subjects and data collected to perform statistical analysis

End point values	Solithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: 10 <sup>6</sup> cells/ml sputum				
arithmetic mean (standard error)	2.47 (± 0.76)	5.30 (± 1.21)		

### Statistical analyses

No statistical analyses for this end point

### Primary: Change in sputum neutrophil counts from baseline

End point title	Change in sputum neutrophil counts from baseline <sup>[2]</sup>
End point description:	

End point type	Primary
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End point timeframe:

Measurements taken at baseline and 28 days after solithromycin or placebo

Notes:

[2] - 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: Due to early termination of the study, there were too few subjects and data collected to perform statistical analysis



End point values	Solithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: 10 <sup>6</sup> cells/ml				
arithmetic mean (standard error)	-1.39 (± 0.73)	1.64 (± 0.86)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Sputum CXCL8

End point title	Sputum CXCL8
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End point description:

End point type	Secondary
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End point timeframe:

Sputum levels of CXCL8 after 28 days with either solithromycin or placebo

End point values	Solithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: ng/ml				
arithmetic mean (standard error)	2.99 (± 0.76)	4.29 (± 0.43)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: CXCL8 Nasal Epithelial Lining Fluid

End point title	CXCL8 Nasal Epithelial Lining Fluid
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End point description:

End point type	Secondary
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End point timeframe:

Nasal fluid CXCL8 measurements after 28 days with either Solithromycin or placebo

End point values	Solithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: ng/ml				
arithmetic mean (standard error)	1.39 ( $\pm$ 0.58)	5.14 ( $\pm$ 1.6)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Small airway resistance (R5-R20)

End point title	Small airway resistance (R5-R20)
End point description:	
End point type	Secondary
End point timeframe:	
Measurement 28 days after solithromycin or placebo	

End point values	Solithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: kPaL-1.s				
arithmetic mean (standard error)	0.31 ( $\pm$ 0.06)	0.21 ( $\pm$ 0.05)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect of solithromycin and placebo on CAT score

End point title	Effect of solithromycin and placebo on CAT score
End point description:	
End point type	Secondary
End point timeframe:	
Measurement taken after 28 days with either solithromycin or placebo	

End point values	Solithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Score				
arithmetic mean (standard error)	16 ( $\pm$ 4)	15 ( $\pm$ 5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect on lung function (FEV1 % predicted)

End point title	Effect on lung function (FEV1 % predicted)
End point description:	
End point type	Secondary
End point timeframe:	
Measurement 28 days after solithromycin or placebo	

End point values	Solithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: % predicted				
arithmetic mean (standard error)	46 ( $\pm$ 2)	44 ( $\pm$ 5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect on lung function (FEV1)

End point title	Effect on lung function (FEV1)
End point description:	
End point type	Secondary
End point timeframe:	
Measurements taken after 28 days with either solithromycin or placebo	

<b>End point values</b>	Solithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: litres				
arithmetic mean (standard error)	1.13 ( $\pm$ 0.16)	1.05 ( $\pm$ 0.08)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time of informed consent up till discharge from the study

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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### Reporting groups

Reporting group title	Solithromycin
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Solithromycin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
Elevated liver tests	Additional description: Deranged liver function tests		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Solithromycin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	1 / 6 (16.67%)	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	

Flatulence			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Epigastric discomfort			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastro-oesophageal reflux			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Derranged LFTs			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Puffy eyes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2015	Amendment 1 was introduced after MHRA review, to update the reference safety information, to include additional criteria for drug discontinuation and to ensure appropriate reporting of SAEs. Appendix B was added to include safety information from the Phase 2 CAPB study with a listing of serious adverse drug reactions. The study procedures included new drug discontinuation criteria based on laboratory findings of increased hepatic transaminases, QT prolongation > 500 ms or change from baseline > 60 ms, increases in heart rate > 120 bpm or change from baseline > 30 bpm, and adverse events associated with inhibition of nicotinic acetylcholine receptors. Additional detail was incorporated to describe procedures for reporting of SAEs to regulatory authorities.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was terminated early due to cholestatic hepatitis in one subject and ALT elevation in two others during or following solithromycin dosing. Data suggested a trend towards reduced sputum and neutrophil numbers but data set is too small.

Notes: