Clinical trial results:
An open label trial of azithromycin in chronic productive cough

Summary

EudraCT number	2013-002938-20
Trial protocol	GB
Global end of trial date	15 July 2016

Results information

Result version number	v1 (current)
This version publication date	24 March 2019
First version publication date	24 March 2019

Trial information

Trial identification

Sponsor protocol code	13031

Additional study identifiers

ISRCTN number	ISRCTN93221282
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	Jubilee campus, Nottingham, United Kingdom, NG51PB
Public contact	Tim Harrison, University of Nottingham, 44 1158231714, tim.harrison@nottingham.ac.uk
Scientific contact	Tim Harrison, University of Nottingham, 44 1158231714, tim.harrison@nottingham.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	15 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2016
Global end of trial reached?	Yes
Global end of trial date	15 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a singlecentre study with detailed description of baseline clinicopathological features followed by an openlabel trial of 12weeks of lowdose azithromycin (250mg thrice weekly) in subjects with idiopathic chronic productive cough.
The main aims were to describe the baseline clinicopathological features of the patients and identify responders and nonresponders to 12week lowdose azithromycin, using change in Leicester Cough Questionnaire (LCQ) as the primary outcome.

Protection of trial subjects:

Patients with a productive cough of ≥3 months duration who had not smoked for ≥10 years with a <20 packyear smoking history were recruited from respiratory clinic if initial investigations found no cause for their symptoms. Subjects were excluded if they had evidence of immunodeficiency, established bronchiectasis on HRCT, history of inhaled irritant exposure, a contraindication to azithromycin treatment (prolonged QT interval on electrocardiogram (ECG)/significant cardiac pathology or liver function tests >2× the upper normal limit) or documented macrolide hypersensitivity. The study was approved by a local Research Ethics Committee (Ref 13/YH/0245). All participants meeting the inclusion criteria attended a baseline visit where written informed consent was obtained. Investigations were carried out over five study visits

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2014
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: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between January 2014 and January 2016, 102 eligible subjects were identified. Fiftyseven of these were already taking azithromycin or another longterm antibiotic and 15 declined the study. Diagnosis of asthma was based on a previous clinical diagnosis.

Pre-assignment

Screening details:

Selection criteria for patients with chronic productive cough:
- Age 18 and over
- Male or female
- Non-smokers for 10 years and <20 pack year equivalents in total
- Persistent productive cough for > 3 months in duration

Exclusion criteria for patients with chronic productive cough:
- History of obvious inhaled irritant exposure
- Evidence

Pre-assignment period milestones

Number of subjects started	30
Number of subjects completed	30

Period 1

Period 1 title	Visit 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All participants

Arm description:

Results are given for all participants whom received Azithromycin treatment per protocol

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

Dosage and administration details:

Azithromycin capsules 250mg 3 times a week for 12 weeks.

Number of subjects in period 1	All participants
Started	30
Completed	30

Period 2	
Period 2 title	Visit 2: Bronchoscopy
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All particiants

Arm description:

Results are given for all participants whom received Azithromycin treatment per protocol

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

Dosage and administration details:

Azithromycin capsules 250mg 3 times a week for 12 weeks.

Number of subjects in period 2	All particiants
Started	30
Completed	30

Period 3	
Period 3 title	Visit 3: Safety
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All participants

Arm description:

Results are given for all participants whom received Azithromycin treatment per protocol

Arm type	Experimental

Investigational medicinal product name	Azithromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Azithromycin capsules 250mg 3 times a week for 12 weeks.

Number of subjects in period 3	All participants
Started	30
Completed	29
Not completed	1
Adverse event, non-fatal	1

Period 4

Period 4 title	Visit 4: Post treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All participants

Arm description:

Results are given for all participants whom received Azithromycin treatment per protocol

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

Dosage and administration details:

Azithromycin capsules 250mg 3 times a week for 12 weeks.

Number of subjects in period 4	All participants
Started	29
Completed	29

Period 5	
Period 5 title	Visit 5: Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All participants

Arm description:

Results are given for all participants whom received Azithromycin treatment per protocol

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

Dosage and administration details:

Azithromycin capsules 250mg 3 times a week for 12 weeks.

Number of subjects in period 5	All participants
Started	29
Completed	26
Not completed	3
Lost to follow-up	3

Baseline characteristics

Reporting groups

Reporting group title	Visit 1

Reporting group description: -

Reporting group values	Visit 1	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	30	30	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age of whole cohort			
Units: years			
arithmetic mean	57		
full range (min-max)	25 to 77	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	13	13	

Subject analysis sets

Subject analysis set title	Responders versus non-responders
Subject analysis set type	Full analysis

Subject analysis set description:

Particoants were split onot those whom responded to the treatment and those who did not for analyses

Reporting group values	Responders versus non-responders		
Number of subjects	22		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			

Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age of whole cohort			
Units: years arithmetic mean full range (min-max)	 56 25 to 77		
Gender categorical Units: Subjects			
Female Male	15 7		

End points

End points reporting groups

Reporting group title	All participants
Reporting group description:	
Results are given for all participants whom received Azithromycin treatment per protocol	
Reporting group title	All particiants
Reporting group description:	
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Reporting group description:	
Results are given for all participants whom received Azithromycin treatment per protocol	
Subject analysis set title	Responders versus non-responders
Subject analysis set type	Full analysis
Subject analysis set description:	
Particoants were split onot those whom responded to the treatment and those who did not for analyses	

Primary: Diff LCQ score v1 to v4

End point title	Diff LCQ score v1 to v4
End point description:	
End point type	Primary
End point timeframe:	
Median difference in LCQ score between visit 1 and visit 4	

End point values	All participants	All participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: LCQ score				
median (inter-quartile range (Q1-Q3))	11.5 (7.8 to 18.2)	17.8 (14.2 to 20.1)		

Statistical analyses

Statistical analysis title	Change in LCQ v1 to v4
Comparison groups	All participants v All participants

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.00001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.3
upper limit	6.3

Secondary: Difference in 24h sputum volume ml

End point title	Difference in 24h sputum volume ml
End point description:	

End point type	Secondary
End point timeframe:	
Difference between visit 1 and visit 4	

End point values	All participants	All participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: mls				
median (inter-quartile range (Q1-Q3))	7.9 (6.2 to 11.7)	2.1 (0 to 7.2)		

Statistical analyses

Statistical analysis title	Diff sputum volume V1 to V4
Comparison groups	All participants v All participants
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	-5.8

Secondary: FE Nitrous Oxide level ppb

End point title	FE Nitrous Oxide level ppb
End point description:	

End point type	Secondary
End point timeframe:	
Difference between v1 and v4	

End point values	All participants	All participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: ppb	18	12		

Statistical analyses

Statistical analysis title	Diff FE no level V1 to V4
Comparison groups	All participants v All participants
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.009
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	-6.5

Secondary: FEV (L)

End point title	FEV (L)
End point description:	

End point type	Secondary
End point timeframe:	
Difference between visit 1 and visit 4	

End point values	All participants	All participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: Litres				
arithmetic mean (standard deviation)	2.77 (± 0.99)	2.75 (± 1)		

Statistical analyses

Statistical analysis title	Diff FEV V1 to V4
Comparison groups	All participants v All participants
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout the trial	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	1.0
Reporting groups	
Reporting group title	All participants
Reporting group description: Azithromycin 3x weekly for 12 weeks	

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)		
General disorders and administration site conditions			
Periorbital oedema			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported