Clinical trial results:
Proof of Concept Evaluation of Drug-Device Interaction with aclidinium bromide via Genuair® and tiotropium bromide via HandiHaler® in COPD using Impulse Oscillometry

Summary

EudraCT number	2013-003594-99
Trial protocol	GB
Global end of trial date	09 July 2015

Results information

Result version number	v1 (current)
This version publication date	21 July 2016
First version publication date	21 July 2016

Trial information

Trial identification

Sponsor protocol code	2013RC09

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02039050
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Tayside Medical Sciences Centre on behalf of the University of Dundee & NHS Tayside
Sponsor organisation address	Residency Block, Level 3, Ninewells Hospital, George Pirie Way, Dundee, United Kingdom, DD1 9SY
Public contact	Arvind Manoharan, University of Dundee, 1382383235 +441382383235, a.d.manoharan@dundee.ac.uk
Scientific contact	Arvind Manoharan, University of Dundee, 1382383235 +441382383235, a.d.manoharan@dundee.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	03 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2015
Global end of trial reached?	Yes
Global end of trial date	09 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the chronic dosing impact of drug-device interaction between tiotropium and aclidinium on early morning trough bronchodilator response using impulse oscillometry in patients with COPD taking inhaled corticosteroids/long-acting beta agonists combination therapy.

Protection of trial subjects:

Subjects were recruited from a database of volunteers who had agreed to be contacted with regard to participating in departmental research. Subjects received a written information sheet (PIS) with details of trial requirements, and had this for at least 24 hours before attending for a screening visit. They were encouraged to discuss the possibility of participation with study staff and others.
Informed consent was obtained before any protocol-specific procedures were carried out. Subjects were given every opportunity to clarify points they did not understand, and ask for more information. It was emphasized that the subject could withdraw consent to participate at any time without loss of benefits to which they otherwise would be entitled. The Chief Investigator could also withdraw a participant at any point if they felt it would be unsafe or inappropriate for the subject to continue. An informed consent form was signed and dated by the subject and the person taking consent, and the volunteer received a copy.
Subjects were only selected if they met the pre-determined inclusion criteria.
Medical history and concomitant medications were reviewed by a medically qualified person to confirm it was safe for the subject to receive the study drug. A physical examination was conducted before randomisation.
Participants received an emergency mobile phone number, carried by a study doctor 24 hours a day, to contact if they experienced any problems.

Background therapy:

Any participants taking a LAMA at initial screening will have this stopped during the 1 week run-in period.
Participants will continue on their ICS/LABA combination inhaler throughout the study but withhold the ICS/LABA for 12 hours prior to the study visits.
Participants who are on theophylline can continue with theophylline throughout the study but will need to withhold the medication for 24 hours prior to study visits.

Evidence for comparator:

There are potentially important differences between available LAMA's for the treatment of COPD which appertain to the unique drug–device interaction when comparing dry powder formulations, namely Spiriva HandiHaler and Eklira Genuair. Firstly there is more homogeneous lung deposition throughout the lung with Eklira Genuair compared to Spiriva HandiHaler(1), which along with better small airways delivery, should translate into an improved bronchodilator response. Furthermore positive feedback from the green light system in terms of peak inspiratory flow with Eklira Genuair(2), is likely to reinforce correct inhaler use and hence more consistent dose delivery.
Secondly at trough coinciding with the end of the usual dosing interval – i.e. comparing 12 hours for Eklira Genuair and 24 hours with Spiriva HandiHaler, there is likely to be a superior bronchodilator response.(3) This is likely to assume even greater relevance for patients throughout the night time period, such that patients will perceive improved control on waking, which in turn is likely to result in a better response for the following day time period i.e. better mornings = better days. Taken together this unique device-drug interaction is likely to produce improved long term disease control with Eklira Genuair.
One possible way to detect such improvements in bronchodilator response

in COPD is to use impulse oscillometry (IOS), which is an effort independent technique measuring lung resistance and compliance at tidal volume –i.e. this requires minimal patient cooperation.(4) In this regard effort dependent tests such as spirometry accentuate forced expiratory volume and pressure dependent airway closure which occurs in COPD . This in turn results in an attenuated signal for bronchodilator response when comparing spirometry and IOS.(5) Moreover IOS permits the discrimination between central and peripheral airway resistance and reactance. Thus IOS is ideally suited to demonstrate th

Actual start date of recruitment	08 May 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: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	6
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from May 2014 until May 2015. A total of 13 subjects completed the study.

Pre-assignment

Screening details:

Subjects were assessed at screening against pre-defined inclusion and exclusion criteria. Eligible subjects entered a 1-3 week run-in period.

Pre-assignment period milestones

Number of subjects started	22
Intermediate milestone: Number of subjects	Screening visit: 22
Number of subjects completed	13

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Unreliable data: 1
Reason: Number of subjects	Did not meet inclusion criteria: 7
Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	No
Arm title	tiotropium

Arm description:

Patients were randomized to tiotropium (Spiriva HandiHaler, Boehringer, Bracknell, UK) 18 microgram bid

Arm type	Active comparator
Investigational medicinal product name	tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

18 (1 puff) micrograms once daily

Arm title	aclidinium

Arm description:

Patients were randomized to either ACL (Eklira Genuair, Astra Zeneca, Luton, UK) 322 microgram bid

Arm type	Experimental

Investigational medicinal product name	aclidinium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

322 micrograms (2 puff) bid

Number of subjects in period 1	tiotropium	aclidinium
Started	13	13
Completed	13	13

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall trial
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period refers to the number of participants who completed the study and included in the final analysis.
Enrolled participants include screen fails.

Reporting group values	Overall trial	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	
From 65-84 years	10	10	
Age continuous Units: years			
arithmetic mean	69		
full range (min-max)	59 to 80	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	10	10	
Post-bronchodilator FEv1 Units: Percentage predicted			
arithmetic mean	52		
standard deviation	± 11	-	

End points

End points reporting groups	
Reporting group title	tiotropium
Reporting group description:	
Patients were randomized to tiotropium (Spiriva HandiHaler, Boehringer, Bracknell, UK) 18 microgram bid	
Reporting group title	aclidinium
Reporting group description:	
Patients were randomized to either ACL (Eklira Genuair, Astra Zeneca, Luton, UK) 322 microgram bid	

Primary: Change in trough R5	
End point title	Change in trough R5
End point description:	
End point type	Primary
End point timeframe:	
1 to 2 weeks	

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: kPa L-1 s				
number (not applicable)	-0.03	-0.07		

Statistical analyses

Statistical analysis title	Paired Student's t-test
Statistical analysis description:	
Paired Student's t-test were used to compare between treatment effects after each chronic dosing.	
Comparison groups	tiotropium v aclidinium
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05 [2]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - The study was powered at 80% to detect a 0.1 kPa L-1 s difference in the the primary outcome of trough R5

[2] - Alpha error of 0.05 (two-tailed)

Secondary: Change in trough R5-R20

End point title	Change in trough R5-R20

End point description:

End point type	Secondary

End point timeframe:
1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: kPa L-1 s				
number (not applicable)	-0.01	-0.06		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in trough FEV1

End point title	Change in trough FEV1

End point description:

End point type	Secondary

End point timeframe:
1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: litre(s)				
number (not applicable)	0.15	0.11		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in trough FEF25-75

End point title	Change in trough FEF25-75

End point description:

End point type	Secondary

End point timeframe:

1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: L s-1				
number (not applicable)	0.06	0.02		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 6MWT Distance

End point title	Change in 6MWT Distance

End point description:

End point type	Secondary

End point timeframe:

1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: metre				
number (not applicable)	9	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SGRQ (total score)

End point title	Change in SGRQ (total score)

End point description:

End point type	Secondary

End point timeframe:

1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: Units				
number (not applicable)	-7.31	-7.35		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in trough R20

End point title	Change in trough R20

End point description:

End point type	Secondary

End point timeframe:

1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: kPa L s-1				
number (not applicable)	-0.02	-0.01		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in trough X5

End point title	Change in trough X5

End point description:

End point type	Secondary

End point timeframe:

1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: kPa L s-1				
number (not applicable)	0.05	0.03		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in trough RF

End point title	Change in trough RF

End point description:

End point type	Secondary

End point timeframe:

1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: hertz				
number (not applicable)	-2.77	-2.22		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in trough AX

End point title	Change in trough AX

End point description:

End point type	Secondary

End point timeframe:

1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: kPa L-1				
number (not applicable)	-0.55	-0.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in trough FVC

End point title	Change in trough FVC

End point description:

End point type	Secondary

End point timeframe:

1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: litre(s)				
number (not applicable)	0.24	0.28		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in trough RVC

End point title	Change in trough RVC

End point description:

End point type	Secondary

End point timeframe:

1 to 2 weeks

End point values	tiotropium	aclidinium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: litre(s)				
number (not applicable)	0.22	0.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs and SAEs were recorded from the time a participant consented to join the study until the last study visit.

Adverse event reporting additional description:

Subjects were asked about the occurrence of AEs at each study visit and received training on how to record AEs and concomitant medications. All AEs were recorded on subject-specific logs in the CRFs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Completed subjects

Reporting group description: -

Serious adverse events	Completed subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Completed subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)		
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Angina pectoris			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Surgical and medical procedures			

Oral surgery			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eye disorders			
Vision blurred	Additional description: Vision disturbance		
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Breathlessness Short of breath		
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 14 (7.14%)		
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