Clinical trial results:
Effects of ultra-long acting bronchodilator therapy assessed by impulse oscillometry in smoking asthmatics taking inhaled corticosteroids

Summary

EudraCT number	2014-005317-23
Trial protocol	GB
Global end of trial date	22 May 2019

Results information

Result version number	v1 (current)
This version publication date	25 November 2020
First version publication date	25 November 2020

Trial information

Trial identification

Sponsor protocol code	2013RC06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02682862
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Dundee - NHS Tayside
Sponsor organisation address	Residency Block, Level 3, Ninewells Hospital, George Pirie Way, Dundee, United Kingdom, DD1 9SY
Public contact	General Enquiries, Scottish Centre for Respiratory Research, 44 (0)1382 383902, scrr@dundee.ac.uk
Scientific contact	General Enquiries, Scottish Centre for Respiratory Research, 44 (0)1382 383902, scrr@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	22 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 May 2019
Global end of trial reached?	Yes
Global end of trial date	22 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of olodaterol alone versus olodaterol plus tiotropium given once daily as add-on therapy to pre-existing inhaled corticosteroids using impulse oscillometry in smoking asthmatics

Protection of trial subjects:

The study Sponsor carried out a study risk assessment before issuing approval. The study was approved by the East of Scotland Research Ethics Service (Ref: 15/ES/0032). Informed consent was obtained from all participants. Participants were checked against all inclusion and exclusion criteria and only participants deemed clinically stable were recruited into the study. A medically-qualified person confirmed that it was safe for the participant to receive the IMP. Participants were issued a peak flow and symptom diary to assess clinical stability throughout the study. Participants were also issued an out-of-hours contact card with the mobile number carried by medical staff for advice if they encountered any adverse effects. One week after the end of each treatment period, patients were contacted by phone as a safety follow-up.

Background therapy:

After the screening visit, participants entered a 2-4 week run-in period when LABA or LAMA were stopped and participants' ICS dose was rounded to equivalent reference ICS as HFA-BDP (Clenil Modulite pMDI). This dose of Clenil was then continued unchanged throughout the study.

Evidence for comparator:

We used the LABA olodaterol (OLO), and the combination of olodaterol with the LAMA tiotropium (OLO/TIO) both delivered via the soft mist Respimat inhaler. The rationale for choosing the Respimat device was that it was possible to deliver the OLO and OLO/TIO via the same device.

Actual start date of recruitment	11 July 2016
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: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	29
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subject recruitment began 11 July 2016 and the study completed on 22 May 2019. Of the 29 patients screened, 17 were randomised and 16 completed per protocol and were included in the final analysis.

Pre-assignment

Screening details:

Diagnosis of persistent asthma, current smokers, age 18-65 years, taking at least 400µg per day of ICS (as HFA-BDP Clenil equivalent dose). Patients with COPD or ACO were excluded. Patients who had an asthma exacerbation requiring systemic corticosteroids within 1 month of screening or requiring hospital admission within 3 months were excluded.

Pre-assignment period milestones

Number of subjects started	29
Number of subjects completed	17

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did Not Meet Inclusion Criteria: 9
Reason: Number of subjects	Worsening Asthma Symptoms During Run-In: 3

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 as this was an open-label study.

Arms

Are arms mutually exclusive?	No
Arm title	Olodaterol

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Olodaterol
Investigational medicinal product code	
Other name	Striverdi Respimat
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Participants inhaled 2 puffs (2.5 micrograms/puff) of olodaterol once daily in the morning for 2 - 4 weeks.

Arm title	Olodaterol-Tiotropium

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Olodaterol-Tiotropium
Investigational medicinal product code	
Other name	Spiolto Respimat
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Participants inhaled 2 puffs (2.5 micrograms/2.5micrograms per puff) of olodaterol-tiotropium once daily in the morning for 2 - 4 weeks.

Number of subjects in period 1	Olodaterol	Olodaterol-Tiotropium
Started	16	17
Completed	16	16
Not completed	0	1
Unable to comply with procedures of the protocol	-	1

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 worldwide number enrolled is the number of subjects screened into the study (29). The number of subjects in the baseline period is the number who were randomised into the study (17). Of these 17 subjects, 16 completed the study per protocol and were able to be analysed.

Reporting group values	Overall Trial	Total	
Number of subjects	17	17	
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)	17	17	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	42.41		
standard deviation	± 11.72	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	7	7	

End points

End points reporting groups

Reporting group title	Olodaterol
Reporting group description: -	
Reporting group title	Olodaterol-Tiotropium
Reporting group description: -	
Subject analysis set title	Completed Subjects
Subject analysis set type	Per protocol
Subject analysis set description:	
Sixteen (16) current smokers with persistent asthma who completed both arms of the study per protocol.	

Primary: Total Airway Resistance (R5)

End point title	Total Airway Resistance (R5)
End point description:	
End point type	Primary
End point timeframe:	
2-4 weeks	

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: kPa/l/s				
arithmetic mean (confidence interval 95%)				
Pooled baseline	0.58 (0.51 to 0.65)	0.58 (0.51 to 0.65)		
Peak first dose	0.44 (0.37 to 0.51)	0.43 (0.37 to 0.49)		
Peak last dose	0.45 (0.37 to 0.52)	0.44 (0.36 to 0.51)		
Final trough	0.56 (0.47 to 0.66)	0.51 (0.42 to 0.59)		

Statistical analyses

Statistical analysis title	Repeated measures ANOVA
Comparison groups	Olodaterol v Olodaterol-Tiotropium

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA

Secondary: FEV1

End point title	FEV1

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: litre(s)				
arithmetic mean (standard error)				
Pooled baseline	2.40 (± 0.18)	2.40 (± 0.18)		
Peak first dose	2.64 (± 0.19)	2.65 (± 0.20)		
Peak last dose	2.70 (± 0.19)	2.74 (± 0.18)		
Final trough	2.53 (± 0.18)	2.60 (± 0.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEF 25-75

End point title	FEF 25-75

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: L/s				
arithmetic mean (standard error)				
Pooled baseline	1.46 (± 0.17)	1.46 (± 0.17)		
Peak first dose	1.79 (± 0.20)	1.78 (± 0.23)		
Peak last dose	1.82 (± 0.21)	1.85 (± 0.21)		
Final trough	1.58 (± 0.18)	2.51 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: FVC

End point title	FVC

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: litre(s)				
arithmetic mean (standard error)				
Pooled baseline	3.49 (± 0.20)	3.49 (± 0.20)		
Peak first dose	3.65 (± 0.21)	3.63 (± 0.21)		
Peak last dose	3.71 (± 0.21)	3.77 (± 0.20)		
Final trough	3.59 (± 0.21)	3.69 (± 0.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: R20

End point title	R20

End point description:

End point type	Secondary

End point timeframe:
2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: kPa/l/s				
arithmetic mean (standard error)				
Pooled baseline	0.42 (± 0.02)	0.42 (± 0.02)		
Peak first dose	0.36 (± 0.02)	0.35 (± 0.02)		
Peak last dose	0.36 (± 0.02)	0.36 (± 0.02)		
Final trough	0.41 (± 0.02)	0.39 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: R5-R20

End point title	R5-R20

End point description:

End point type	Secondary

End point timeframe:
2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: kPa/l/s				
arithmetic mean (standard error)				
Pooled baseline	0.17 (± 0.03)	0.17 (± 0.03)		
Peak first dose	0.09 (± 0.02)	0.08 (± 0.02)		
Peak final dose	0.09 (± 0.02)	0.08 (± 0.02)		
Final trough	0.15 (± 0.03)	0.12 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: AX

End point title	AX

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: kPa/l				
arithmetic mean (standard error)				
Pooled baseline	1.81 (± 0.32)	1.81 (± 0.32)		
Peak first dose	0.84 (± 0.23)	0.75 (± 0.21)		
Peak last dose	0.80 (± 0.23)	0.70 (± 0.22)		
Final trough	1.54 (± 0.40)	1.16 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fres

End point title	Fres

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: hertz				
arithmetic mean (standard error)				
Pooled baseline	19.75 (± 1.19)	19.75 (± 1.19)		
Peak first dose	14.66 (± 1.17)	14.48 (± 1.15)		
Peak last dose	14.09 (± 1.27)	13.69 (± 1.19)		
Final trough	18.40 (± 1.54)	16.11 (± 1.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: X5

End point title	X5

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: kPa/l/s				
arithmetic mean (standard error)				
Polled baseline	-0.24 (± 0.03)	-0.24 (± 0.03)		
Peak first dose	-0.17 (± 0.03)	-0.15 (± 0.02)		
Peak last dose	-0.16 (± 0.02)	-0.15 (± 0.02)		
Final trough	-0.21 (± 0.03)	-0.19 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptoms AM

End point title	Symptoms AM

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: units				
arithmetic mean (standard error)				
Pooled baseline	0.71 (± 0.12)	0.63 (± 0.10)		
End of treatment	0.51 (± 0.14)	0.39 (± 0.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptoms PM

End point title	Symptoms PM

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: units				
arithmetic mean (standard error)				
Pooled baseline	0.63 (± 0.10)	0.63 (± 0.10)		
End of treatment	0.31 (± 0.12)	0.27 (± 0.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reliever AM

End point title	Reliever AM

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: puffs				
arithmetic mean (standard error)				
Pooled baseline	1.05 (± 0.20)	10.5 (± 0.20)		
End of treatment	0.55 (± 0.17)	0.45 (± 0.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reliever PM

End point title	Reliever PM

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: puffs				
arithmetic mean (standard error)				
Pooled baseline	0.92 (± 0.20)	0.91 (± 0.20)		
End of treatment	0.55 (± 0.15)	0.33 (± 0.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: PEF AM

End point title	PEF AM

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: L/min				
arithmetic mean (standard error)				
Pooled baseline	369 (± 26)	369 (± 26)		
End of treatment	408 (± 34)	420 (± 31)		

Statistical analyses

No statistical analyses for this end point

Secondary: PEF PM

End point title	PEF PM

End point description:

End point type	Secondary

End point timeframe:

2-4 weeks

End point values	Olodaterol	Olodaterol-Tiotropium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: L/min				
arithmetic mean (standard error)				
Pooled baseline	388 (± 31)	388 (± 31)		
End of treatment	408 (± 34)	420 (± 31)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time a participant consented to join the study until the last study visit.

Adverse event reporting additional description:

Participants received training on how to record adverse events on trial-specific diary cards. At each study visit, participants were asked about the occurrence of any adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Received IMP

Reporting group description: -

Serious adverse events	Received IMP		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Irritable Bowel Syndrome			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Received IMP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 17 (88.24%)		
Injury, poisoning and procedural complications			
Limb Injury			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all) Sciatica subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 8 1 / 17 (5.88%) 3 1 / 17 (5.88%) 3 3 / 17 (17.65%) 3 1 / 17 (5.88%) 1		
General disorders and administration site conditions Influenza-like illness subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2 1 / 17 (5.88%) 1		
Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastrointestinal disorders Haemorrhoids subjects affected / exposed occurrences (all) Tongue Blistering	1 / 17 (5.88%) 1		

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 6		
Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Cough subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3		
Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Musculoskeletal and connective tissue disorders			
Back Pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Arthralgia subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Arthritis			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Infections and infestations Oral Candidiasis subjects affected / exposed occurrences (all) Abscess subjects affected / exposed occurrences (all) Genital infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	 2 / 17 (11.76%) 2 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2015	REC Amendment - Amendment to notify REC of changes made during application to MHRA for initial study approval.
02 August 2016	REC & MHRA Amendment - Amendment to specify that Clenil Modulite is the steroid inhaler to be used as background medication during the study.
03 April 2018	REC Amendment - Amendment for use of additional sources for patient recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported