Clinical trial results:
Pilot study to evaluate whether treating persistent small airway dysfunction with extra-fine HFA-Beclometasone results in improved asthma control.

Summary

EudraCT number	2012-003923-39
Trial protocol	GB
Global end of trial date	25 June 2018

Results information

Result version number	v1 (current)
This version publication date	22 June 2019
First version publication date	22 June 2019

Trial information

Trial identification

Sponsor protocol code	2012RC16

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01894048
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	Professor Brian Lipworth, Scottish Centre for Respiratory Research, 44 01382 383188, b.j.lipworth@dundee.ac.uk
Scientific contact	Professor Brian Lipworth, Scottish Centre for Respiratory Research, 44 01382 383188, b.j.lipworth@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	25 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2018
Global end of trial reached?	Yes
Global end of trial date	25 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess patient reported outcomes after switching from large to small particle beclometasone dipropionate (BDP) in persistent asthma.

Protection of trial subjects:

The study was approved by the East of Scotland Research Ethics Service (EoSRES).

Potential participants received a written Participant Information Sheet (PIS) detailing the requirements of the trial and the extent of their participation before attending for a screening visit. Participants were given at least 24 hours to read the PIS and were encouraged to discuss their potential study participation with others, such as their doctor, family or friends. At the study screening visit, a member of the research team discussed the PIS with the participant and answered any questions posed. Written informed consent was obtained prior to any study-specific procedures.

Participants were only selected if they fulfilled the pre-determined inclusion criteria.

Background therapy:

Patients were enrolled with persistent asthma, taking steps 2, 3 or 4 of British Thoracic Society guidelines, with an ICS dose up to 2000ug/day (Clenil equivalent dose) of large particle ICS with or without long acting β2 adrenoceptor agonist (LABA), long acting muscarinic antagonists (LAMA) or leukotriene receptor antagonist (LTRA).
Patients were requested to stop any second line controller therapy and were then converted to a reference large particle ICS as Clenil pMDI for the subsequent step down and run-in phase.

Evidence for comparator: -

Actual start date of recruitment	28 October 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: 74
Worldwide total number of subjects	74
EEA total number of subjects	74

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)	66
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subject recruitment began 28 October 2013 and the study completed on 25 June 2018. Of the 74 patients screened, 26 were randomised and 24 completed per protocol and were included in the final analysis.

Pre-assignment

Screening details:

Males and females with persistent asthma, aged 18-70 years, on inhaled corticosteroid (ICS) dose up to 2000 mcg/day (Clenil equivalent dose) of large particle ICS with or without long acting β2 agonist (LABA), long acting muscarinic antagonists (LAMA) or leukotriene receptor antagonist (LTRA), FEV1 at least 60% predicted, ACQ at least 1.0.

Pre-assignment period milestones

Number of subjects started	74
Number of subjects completed	26

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did Not Meet Inclusion Criteria: 44
Reason: Number of subjects	Adverse event, non-fatal: 2
Reason: Number of subjects	Elective Procedure Scheduled: 1
Reason: Number of subjects	Family Bereavement: 1

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Qvar (Baseline)
Arm description: -	
Arm type	Baseline Measurements
No investigational medicinal product assigned in this arm	
Arm title	Qvar (8 weeks)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Qvar
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Following their run-in phase, each subject was switched to an equivalent daily dose of Qvar, which was continued unchanged over an 8-week period.

Number of subjects in period 1	Qvar (Baseline)	Qvar (8 weeks)
Started	26	24
Completed	26	24

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 (74). The number of subjects in the baseline period is the number who were then randomised into the study (26). Of these 26 subjects, 24 completed the study per protocol and were able to be analysed.

Reporting group values	Overall Trial	Total	
Number of subjects	26	26	
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)	23	23	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	49.15		
standard deviation	± 16.40	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	10	10	

End points

End points reporting groups

Reporting group title	Qvar (Baseline)
Reporting group description: -	
Reporting group title	Qvar (8 weeks)
Reporting group description: -	

Primary: ACQ

End point title	ACQ
End point description:	
End point type	Primary
End point timeframe:	

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: units				
arithmetic mean (standard error)	1.65 (± 0.08)	1.12 (± 0.12)		

Statistical analyses

Statistical analysis title	Repeated Measures ANOVA

Statistical analysis description:

The null hypothesis proposed is that compared to the post run-in baseline on coarse-particle ICS; there would
be no difference in asthma control (as ACQ) after switching to extra-fine ICS treatment at the equivalent dose. The study was designed with at least 80% power to detect a 0.4 unit change in the primary outcome of ACQ at 8 weeks, assuming a standard deviation of 0.68, with an alpha error (two tailed) of 0.05, requiring at least 23 patients to complete per protocol.

Comparison groups	Qvar (Baseline) v Qvar (8 weeks)
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.12

Secondary: mAQLQ

End point title	mAQLQ

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: units				
arithmetic mean (standard error)	5.34 (± 0.13)	6.03 (± 0.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 (%) predicted

End point title	FEV1 (%) predicted

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: percent				
arithmetic mean (standard error)	86 (± 3)	86 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEF25-75 (%) predicted

End point title	FEF25-75 (%) predicted

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: percent				
arithmetic mean (standard error)	53 (± 5)	53 (± 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: AX (kPa/L)

End point title	AX (kPa/L)

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: kPa/L				
arithmetic mean (standard error)	1.83 (± 0.32)	2.09 (± 0.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: R5 (kPa/L.s)

End point title	R5 (kPa/L.s)

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: kPa/L.s				
arithmetic mean (standard error)	0.57 (± 0.03)	0.61 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: R5-R20 (kPa/L.s)

End point title	R5-R20 (kPa/L.s)

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: kPa/L.s				
arithmetic mean (standard error)	0.17 (± 0.03)	0.19 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: FeNO (ppb)

End point title	FeNO (ppb)

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: ppb				
geometric mean (standard error)	20 (± 2)	24 (± 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Eosinophils

End point title	Eosinophils

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: cells/microlitre				
geometric mean (standard error)	156 (± 22)	179 (± 21)		

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:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: L/min				
arithmetic mean (standard error)	398 (± 27)	409 (± 27)		

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:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: L/min				
arithmetic mean (standard error)	393 (± 28)	406 (± 27)		

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:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: units				
geometric mean (standard error)	0.67 (± 0.11)	0.47 (± 0.12)		

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:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: units				
geometric mean (standard error)	0.69 (± 0.12)	0.48 (± 0.14)		

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:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: puffs/day				
geometric mean (standard error)	0.63 (± 0.18)	0.35 (± 0.13)		

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:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: puffs/day				
geometric mean (standard error)	0.97 (± 0.2)	0.52 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mannitol PD15

End point title	Mannitol PD15

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mg				
geometric mean (standard error)	174 (± 68)	525 (± 217)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mannitol RDR

End point title	Mannitol RDR

End point description:

End point type	Secondary

End point timeframe:

Comparisons were made at baseline after patients were on a constant dose of fine-particle ICS and after 8 weeks of switching to an equivalent dose of extra-fine particle hydrofluoroalkane beclometasone dipropionate (Qvar).

End point values	Qvar (Baseline)	Qvar (8 weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: % fall/mg				
geometric mean (standard error)	0.08 (± 0.03)	0.03 (± 0.01)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) were recorded from the time a participant consented to join the study until the last study visit.

Adverse event reporting additional description:

Participants 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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Completed Per Protocol

Reporting group description: -

Serious adverse events	Completed Per Protocol		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 24 (4.17%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 24 (4.17%)		
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	Completed Per Protocol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 24 (87.50%)		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	19		
Migraine			

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	16		
Oropharyngeal pain			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Tonsillitis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2014	REC & MHRA Amendment - Amendment to enable inclusion of patients already receiving extra-fine particle inhaled corticosteroids.
15 April 2016	REC Amendment - Amendment to seek prospective approval of patient-facing documents.
02 June 2017	REC Amendment - Clarifications of inclusion criteria, notification of new equipment used in study, notification of department name change, changes to study paperwork in line with new guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported