Clinical trial results:
A two-arm, randomised, assessor-blind, parallel group study to evaluate the effect of fluticasone/formoterol breath actuated inhaler (BAI) and Relvar Ellipta DPI on ventilation heterogeneity in subjects with partially controlled or uncontrolled asthma.

Summary

EudraCT number	2015-000801-38
Trial protocol	SE SK
Global end of trial date	14 August 2017

Results information

Result version number	v1 (current)
This version publication date	16 August 2018
First version publication date	16 August 2018

Trial information

Trial identification

Sponsor protocol code	KFL3502

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mundipharma Research Ltd.
Sponsor organisation address	Cambridge Science Park, Cambridge, United Kingdom, CB4 0GW
Public contact	Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.com
Scientific contact	Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.com

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	14 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 August 2017
Global end of trial reached?	Yes
Global end of trial date	14 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate improvement of peripheral airway resistance (R5-R20) from baseline with fluticasone/formoterol breath actuated inhaler (BAI).

Protection of trial subjects:

All subjects were provided with oral and written information describing the nature and duration of the study, its purpose, the procedures to be performed, the potential risks and benefits involved, and any potential discomfort. Each subject was given a copy of the PIS and ICF. The subject was asked to sign and date an ICF prior to any study-specific procedures being performed.

Background therapy:

Subjects already on Seretide Accuhaler 250/50 µg BID at screening underwent a run-in period of 2 weeks during which they continued their Seretide Accuhaler medication. Subjects on equivalent /higher doses of other ICS-LABAs or higher dose of Seretide at screening were also eligible to undergo a run-in of 4 weeks on Seretide Accuhaler 250/50 µg BID.
As well as receiving IMP, all subjects were also provided with Ventolin (salbutamol) as rescue medication at the start of the run-in period to be used as needed during the run in and treatment periods of the study at a dose of up to 8 puffs/day.

Evidence for comparator:

Relvar Ellipta was chosen as a comparator product because it is an approved ICS-LABA combination therapy. Relvar Ellipta is a dry powder inhaler (DPI).

Actual start date of recruitment	14 June 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	Australia: 10
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Slovakia: 59
Country: Number of subjects enrolled	Sweden: 5
Worldwide total number of subjects	103
EEA total number of subjects	86

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)	85
From 65 to 84 years	17
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was carried out at 5 sites in Australia, New Zealand, Slovakia, Sweden and the UK. The first subject first visit was carried out on 14 June 2016 and the last subject last visit was conducted on 14 Aug 2017.

Pre-assignment

Screening details:

240 subjects provided written informed consent and were screened. 103 subjects failed screening: 98 failed screening procedures, 2 withdrew, 2 failed due to administrative reasons, 1 failed due to AE. 34 subjects failed run-in: 2 due to administrative reasons, 2 failed due to AE, 1 was non-compliant and 29 did not meet randomisation crtieria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

Each investigator site had a named, unblinded person who dispensed run-in medication, rescue medication and IMP to subjects. This person was not involved in the assessment of subjects.

Arms

Are arms mutually exclusive?	Yes
Arm title	Fluticasone/formoterol BAI

Arm description:

Fluticasone/formoterol BAI, 125/5, 2 puffs, BID

Arm type	Experimental
Investigational medicinal product name	Fluticasone/formoterol BAI
Investigational medicinal product code	Fluticasone/formoterol BAI
Other name	
Pharmaceutical forms	Inhalation powder, Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

125/5 µg; 2 puffs, twice a day.

Arm title	Relvar Ellipta

Arm description:

Relvar Ellipta, 1 puff, BID

Arm type	Active comparator
Investigational medicinal product name	Fluticasone/vilanterol DPI
Investigational medicinal product code	Relvar Ellipta
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

92/22 µg; 1 puff, once a day.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The study was designed as assessor-blind due to the challenges associated with developing a placebo device for Relvar Ellipta. Nonetheless, because of the objective nature of the primary and key secondary efficacy variables, the subject's knowledge of their treatment was unlikely to influence the

key study outcomes. Furthermore, use of two different devices which require different inspiratory techniques may have created patient confusion leading to more handling errors.

Number of subjects in period 1	Fluticasone/formoterol BAI	Relvar Ellipta
Started	54	49
Completed	51	49
Not completed	3	0
Consent withdrawn by subject	1	-
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Fluticasone/formoterol BAI
Reporting group description:	
Fluticasone/formoterol BAI, 125/5, 2 puffs, BID	
Reporting group title	Relvar Ellipta
Reporting group description:	
Relvar Ellipta, 1 puff, BID	

Reporting group values	Fluticasone/formoterol BAI	Relvar Ellipta	Total
Number of subjects	54	49	103
Age categorical Units: Subjects			
Adults (18-65 years)	45	40	85
66 years and over	9	9	18
Age continuous Units: years			
arithmetic mean	52.1	52.8	
standard deviation	± 12.65	± 13.98	-
Gender categorical Units: Subjects			
Female	34	36	70
Male	20	13	33
Race Units: Subjects			
White	51	46	97
Black or African American	0	2	2
Asian	2	1	3
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	1	0	1
Other	0	0	0
Weight Units: kg			
arithmetic mean	85.25	77.79	
standard deviation	± 19.192	± 16.035	-
Height Units: cm			
arithmetic mean	166.5	163.6	
standard deviation	± 9.99	± 7.51	-
BMI Units: kg/m2			
arithmetic mean	30.66	29.10	
standard deviation	± 6.038	± 5.901	-

End points

End points reporting groups

Reporting group title	Fluticasone/formoterol BAI
Reporting group description: Fluticasone/formoterol BAI, 125/5, 2 puffs, BID	
Reporting group title	Relvar Ellipta
Reporting group description: Relvar Ellipta, 1 puff, BID	

Primary: Change in R5-R20 (peripheral airway resistance) from baseline to week 8

End point title	Change in R5-R20 (peripheral airway resistance) from baseline to week 8
End point description: Peripheral airway resistance (R5-R20) was measured by Impulse Oscillometry as the difference between total airway resistance (R5) and central airway resistance (R20)	
End point type	Primary
End point timeframe: From baseline to week 8.	

End point values	Fluticasone/formoterol BAI	Relvar Ellipta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	49		
Units: kPa/L/s				
least squares mean (confidence interval 95%)	0.01 (-0.026 to 0.039)	-0.02 (-0.059 to 0.013)		

Statistical analyses

Statistical analysis title	Fluticasone/Formoterol vs Relvar Ellipta
Statistical analysis description: Statistical analysis was done using a mixed-model repeated measures (MMRM) analysis of covariance (ANCOVA) with fixed terms for treatment group, visit, treatment*visit interaction, ICS/LABA use at screening (Seretide Accuhaler 250/50 µg BID; other ICS/LABA at Seretide Accuhaler 250/50 µg BID-equivalents; other ICS/LABA or Seretide Accuhaler at dose > Seretide Accuhaler 250/50 µg BID-equivalents) and baseline R5-R20 as a covariate. Multiple Imputation (MI) was employed to account for missing data	
Comparison groups	Fluticasone/formoterol BAI v Relvar Ellipta
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.172 [1]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.072

Notes:

[1] - The primary comparison was change from baseline to week 8.
p=0.693 for the LS mean difference from baseline to week 8 for Fluticasone/Formoterol BAI group.
p=0.210 for the LS mean difference from baseline to week 8 for Relvar Ellipta.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events were recorded from the point at which the Informed Consent was signed until 14 days after the subject left the study. This included new AEs that were reported in the 14 days following the subject's completion/discontinuation visit.

Adverse event reporting additional description:

Only treatment emergent AEs were analysed. A treatment emergent AE was defined as any AE with an onset date on or after the first dose of IMP if the AE was absent before the first dose of IMP, or worsened after the first dose of IMP. This also included AEs with an onset date up to and including 7 days after the last dose of IMP.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Fluticasone/formoterol BAI

Reporting group description:

Fluticasone/formoterol BAI, 125/5, 2 puffs, BID

Reporting group title	Relvar Ellipta

Reporting group description:

Relvar Ellipta, 1 puff, BID

Serious adverse events	Fluticasone/formoterol BAI	Relvar Ellipta	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 54 (5.56%)	1 / 49 (2.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Fluticasone/formoterol BAI	Relvar Ellipta	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 54 (40.74%)	11 / 49 (22.45%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of head and neck			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Humidity intolerance			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 54 (5.56%)	1 / 49 (2.04%)	
occurrences (all)	5	1	

Cough			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Haemoptysis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Nasal polyps			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Blood cholesterol increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased			
subjects affected / exposed	2 / 54 (3.70%)	0 / 49 (0.00%)	
occurrences (all)	2	0	
Lymphocyte count increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Carpal tunnel syndrome			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
VIIth nerve paralysis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 54 (3.70%)	0 / 49 (0.00%)	
occurrences (all)	3	0	
Dyspepsia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Urticaria			

subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 54 (3.70%)	2 / 49 (4.08%)	
occurrences (all)	3	2	
Rhinitis			
subjects affected / exposed	2 / 54 (3.70%)	1 / 49 (2.04%)	
occurrences (all)	2	1	
Bronchitis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Gastroenteritis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Laryngitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			

subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Tracheitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2016	Protocol Amendment No. 1 was required to remove Functional Respiratory Imaging (FRI) as a secondary objective from the protocol. The HDCT scans at Visits 2, 4, 5 and the associated endpoints and analyses were removed from the protocol. This amendment was implemented as the risk:benefit ratio for exposing subjects recruited under this protocol to radiation associated with HDCT scans was considered unfavourable. This decision was made following review of the study protocol by the UK research ethics committee (Cambridge East Research Ethics Committee).
05 January 2017	Protocol Amendment No. 2 was intended to address recruitment challenges in the study without detriment to the scientific quality of the study. The current recruitment rate had been significantly slower than anticipated and this amendment was intended to address the issues which were found to be impacting on this; in this amendment the screening and randomisation inclusion value of IOS R5-R20 were lowered, a second IOS was allowed at screening to mitigate issues associated with subjects failing to withhold medication per the protocol instructions, and the sample size was reduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported