Clinical trial results:
A randomised, open label, two-period, cross-over, multi-centre study to compare correct inhaler handling of fluticasone/ formoterol breath-actuated inhaler (K-Haler®) with that of Symbicort® Turbohaler® in subjects with persistent asthma, ACOS or COPD.

Summary

EudraCT number	2014-004564-38
Trial protocol	GB DE
Global end of trial date	04 July 2017

Results information

Result version number	v1 (current)
This version publication date	18 July 2018
First version publication date	18 July 2018

Trial information

Trial identification

Sponsor protocol code	KFL3501

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sample data: Sample data

Notes:

Sponsors

Sponsor organisation name	Mundipharma Research Limited
Sponsor organisation address	Cambridge Science Park Milton Road, Cambridge, United Kingdom, CB4 0AB
Public contact	Clinical Research Operations, Mundipharma Research Limited, +44 1223424900, info@contact-clinical-trials.com
Scientific contact	Clinical Research Operations, Mundipharma Research Limited, +44 1223424900, 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	04 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2017
Global end of trial reached?	Yes
Global end of trial date	04 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the ability of subjects with asthma, ACOS and COPD to correctly handle the fluticasone/formoterol K-Haler and Symbicort Turbohaler. The objective of the study is to show superiority in correct inhaler handling of fluticasone/ formoterol K-Haler versus Symbicort Turbohaler, following instruction by a health care professional (HCP) as determined by all critical steps being performed correctly 12 weeks after training.

Protection of trial subjects:

Data protection will be carried out in accordance with the Principles of the Data Protection Act (1998) 95/46/EC. This will apply to all study data in whatever format it is collected and recorded. The site may publish or present the results of this protocol subject to the protection of any patentable rights of the Sponsor or its nominee(s) and subject to the protection of the Sponsor's confidential information.

Background therapy:

This study will enroll subjects currently receiving Seretide Accuhaler/Viani Diskus for their asthma or COPD and will allocate them to one of two treatment sequences. Given the utility of combination ICS-LABA therapy a number of combination inhalers containing both ICS and LABA in the same inhaler device have been developed, with both dry powder inhaler (DPI) and pressurised metered dose inhaler (pMDI) presentations available. A third, less widely used device type is the breath-actuated inhaler (BAI), although no ICS-LABA combinations in a BAI are currently marketed. Nonetheless a BAI may be associated with some potential advantages compared to both DPIs and pMDIs. Firstly, BAI device resistance is very low, unlike DPIs which are typically designed with a higher device resistance to encourage the patient to inhale hard thereby de-agglomerating the powder formulation and generating an aerosol. In patients with low inspiratory flow rates, typically the elderly, patients with very severe COPD, young children and patients with exacerbations of their disease, the ability to produce an adequately high negative pressure to generate a powder aerosol may be compromised particularly through a high resistance DPI. Secondly a BAI, which contains a pressurised canister, requires no manual depression of the canister at the time of inhalation, unlike a pMDI. Rather the inhalation maneuver triggers canister actuation. This therefore removes the need for coordination of these two maneuvers (inhalation and canister depression). Thus BAIs have potential advantages over both DPIs and pMDIs which may facilitate successful use in a greater proportion of patients.

Evidence for comparator:

The Symbicort Turbohaler was selected as the comparator in this study as it is a market leading ICS-LABA combination product.

Actual start date of recruitment	22 June 2015
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	Germany: 313
Country: Number of subjects enrolled	United Kingdom: 56

Worldwide total number of subjects	369
EEA total number of subjects	369

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)	275
From 65 to 84 years	94
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

423 subjects with asthma, COPD, or ACOS in both Germany (11 sites) and the UK (1 site) across a broad age range provided written informed consent and were screened.

Pre-assignment

Screening details:

No study procedure was completed until written informed consent was given. Of the 423 subjects, 369 were randomized while 54 subjects failed at screening for various reasons (administrative, failed procedures, lost to follow-up, and withdraw by subject). Of the 369 randomized subjects, 338 subjects completed while 31 subjects discontinued.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

As this is not a blinded study, there is no need for any unblinding procedures.

Arms

Are arms mutually exclusive?	No
Arm title	Fluticasone/Formoterol BAI

Arm description:

Fluticasone/formoterol BAI (K-Haler), 50/5 µg or 125/5µg, 2 actuations bid, via inhalation

Arm type	Experimental
Investigational medicinal product name	Fluticasone/formoterol BAI
Investigational medicinal product code	
Other name	K-Haler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

For subjects using pre-study/washout medication Seretide Accuhaler at 100/50 bid, subject will receive study treatment (K-haler) of 100/10 bid. For subjects using pre-study/washout medication Seretide Accuhaler at 250/50 bid or 500/50 bid, subject will receive study treatment (K-haler) of 250/10 bid.

Arm title	Symbicort Turbohaler

Arm description:

Symbicort Turbohaler (budesonide/formoterol), 100/6 µg or 200/6 µg, 2 actuations bid, via inhalation

Arm type	Active comparator
Investigational medicinal product name	Symbicort Turbohaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

For subjects using pre-study/washout medication Seretide Accuhaler at 100/50 bid, subject will receive study treatment (Symbicort Turbohaler) of 200/12 bid. For subjects using pre-study/washout medication Seretide Accuhaler at 250/50 bid or 500/50 bid, subject will receive study treatment (Symbicort Turbohaler) of 400/12 bid.

Number of subjects in period 1	Fluticasone/Formoterol BAI	Symbicort Turbohaler
Started	369	369
Completed	338	338
Not completed	31	31
Consent withdrawn by subject	15	15
Cannot be trained	1	1
Adverse event, non-fatal	8	8
Lost to follow-up	2	2
Lack of efficacy	2	2
Protocol deviation	3	3

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

As this is not a blinded study, there is no need for any unblinding procedures.

Arms

Are arms mutually exclusive?	No
Arm title	Fluticasone/Formoterol BAI

Arm description:

Fluticasone/formoterol BAI (K-Haler), 50/5 µg or 125/5µg, 2 actuations bid, via inhalation

Arm type	Experimental
Investigational medicinal product name	Fluticasone/formoterol BAI
Investigational medicinal product code	
Other name	K-Haler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

For subjects using pre-study/washout medication Seretide Accuhaler at 100/50 bid, subject will receive study treatment (K-haler) of 100/10 bid. For subjects using pre-study/washout medication Seretide Accuhaler at 250/50 bid or 500/50 bid, subject will receive study treatment (K-haler) of 250/10 bid.

Arm title	Symbicort Turbohaler

Arm description:

Symbicort Turbohaler (budesonide/formoterol), 100/6 µg or 200/6 µg, 2 actuations bid, via inhalation

Arm type	Active comparator
Investigational medicinal product name	Symbicort Turbohaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

For subjects using pre-study/washout medication Seretide Accuhaler at 100/50 bid, subject will receive study treatment (Symbicort Turbohaler) of 200/12 bid. For subjects using pre-study/washout medication Seretide Accuhaler at 250/50 bid or 500/50 bid, subject will receive study treatment (Symbicort Turbohaler) of 400/12 bid.

Number of subjects in period 2	Fluticasone/Formoterol BAI	Symbicort Turbohaler
Started	183	186
Completed	165	173
Not completed	18	13
Consent withdrawn by subject	9	6
Cannot be trained	1	-
Adverse event, non-fatal	4	4
Lost to follow-up	1	1
Lack of efficacy	1	1
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period 1

Reporting group description: -

Reporting group values	Treatment Period 1	Total	
Number of subjects	369	369	
Age categorical			
Demographics, including age categories, was displayed for the full analysis population (N=362).			
Units: Subjects			
>=0 to <=17 years	0	0	
>=18 to <=65 years	274	274	
>65 years	95	95	
Age continuous			
Descriptive statistics of the age of each subject at baseline.			
Units: years			
arithmetic mean	53.5		
standard deviation	± 15.51	-	
Gender categorical			
Units: Subjects			
Female	197	197	
Male	172	172	
Race			
Units: Subjects			
White	365	365	
Black or African American	2	2	
Asian	0	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Other	2	2	

End points

End points reporting groups

Reporting group title	Fluticasone/Formoterol BAI
Reporting group description:	
Fluticasone/formoterol BAI (K-Haler), 50/5 µg or 125/5µg, 2 actuations bid, via inhalation	
Reporting group title	Symbicort Turbohaler
Reporting group description:	
Symbicort Turbohaler (budesonide/formoterol), 100/6 µg or 200/6 µg, 2 actuations bid, via inhalation	
Reporting group title	Fluticasone/Formoterol BAI
Reporting group description:	
Fluticasone/formoterol BAI (K-Haler), 50/5 µg or 125/5µg, 2 actuations bid, via inhalation	
Reporting group title	Symbicort Turbohaler
Reporting group description:	
Symbicort Turbohaler (budesonide/formoterol), 100/6 µg or 200/6 µg, 2 actuations bid, via inhalation	
Subject analysis set title	Randomised Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The randomised population is defined as all randomised subjects.	
Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis population is defined as all randomised subjects who use at least one device (fluticasone/ formoterol K-Haler or Symbicort Turbohaler) and have at least one formal assessment (i.e. beyond the critique of the “practice” attempt).	

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Population is defined as all FAP subjects who complete both treatment periods and who have no other major protocol deviations. Major protocol deviations will be agreed at the Data Review Meeting (DRM).	

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population is defined as all randomised subjects who use at least one device (fluticasone/ formoterol K-Haler or Symbicort Turbohaler).	

Primary: Critical Device Handling Success (OC)

End point title	Critical Device Handling Success (OC)
End point description:	
The number and percentage of subjects that can perform all critical steps correctly when using the inhaler device 12 weeks after training (i.e. from the first attempt at week 12) will be summarized by treatment for the full analysis population. Two-sided 95% confidence intervals (exact Clopper-Pearson intervals for the binomial proportion) for the proportions will also be included in these summaries. This is for the observed case only.	
End point type	Primary
End point timeframe:	
Subjects are assessed using the inhaler device 12 weeks after training (i.e. from the first attempt at week 12).	

End point values	Fluticasone/Formoterol BAI	Symbicort Turbohaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	319	336		
Units: Percentage				
number (confidence interval 95%)				
Successful	94.0 (90.0 to 96.4)	82.4 (77.9 to 86.4)		
Unsuccessful	6.0 (3.6 to 9.1)	17.6 (13.6 to 22.1)		

Statistical analyses

Statistical analysis title	Analysis of Critical Device Handling Success W12

Statistical analysis description:

The logistic regression model will include fixed terms for treatment and period, and subject and centre as random effects. Age and baseline FEV1 will be included as continuous covariates. Kenward-Roger degrees of freedom shall be employed. The statistical model will be used to calculate the odds ratio and 95% confidence interval for the treatment comparison: fluticasone/formoterol BAI (test) versus Symbicort Turbohaler (reference) and p-value from the statistical test will be displayed.

Comparison groups	Fluticasone/Formoterol BAI v Symbicort Turbohaler
Number of subjects included in analysis	655
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.57
upper limit	5.33

Notes:

[1] - As this is a crossover study, the number of subjects is incorrect and should be listed as 351 subjects in the Fluticasone group and 349 subjects in the Symbicort group. EudraCT just adds the numbers up and does not allow you to enter them manually.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Entire Study Period	
Adverse event reporting additional description: Treatment Emergent AEs for Safety Population	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Khaler
Reporting group description: Khaler	
Reporting group title	Symbicort
Reporting group description: Symbicort	

Serious adverse events	Khaler	Symbicort	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 351 (3.13%)	11 / 349 (3.15%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Throat cancer			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accident			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Limb operation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Radiculopathy			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 351 (0.28%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 351 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 351 (0.28%)	0 / 349 (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: 5 %

Non-serious adverse events	Khaler	Symbicort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 351 (3.99%)	18 / 349 (5.16%)	
Infections and infestations			
Viral upper respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 351 (3.99%)	18 / 349 (5.16%)	
occurrences (all)	15	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2015	Protocol Amendment No. 1 amended the acceptable contraceptive measures detailed in the inclusion criteria. Some additional errata and inconsistencies were also corrected in the protocol.
11 June 2015	Protocol Amendment No. 2 amended the criteria for assessment of Symbicort Turbohaler step 7.
13 November 2015	Protocol Amendment No. 3 clarified criteria for discontinuation and corrected an inconsistency in the protocol. It included an additional assessment, at 12 weeks, of a subject's ability to generate an adequate inspiratory flow for the Fluticasone/Formoterol BAI.
16 December 2015	Protocol Amendment No. 4 allowed the inclusion of the same product marketed under a different name in Germany, e.g., Atmadisc Diskus is the same product as Viani Diskus and Seretide Accuhaler.
27 June 2016	Additional exploratory efficacy endpoints were added. The subjects' ability to trigger the Fluticasone/Formoterol BAI for all Fluticasone/Formoterol BAI assessments was assessed rather than only on day 1 at the first post-HCP training assessment and at week 12 prior to HCP training. For the statistical analyses, Step 5 of the Fluticasone/Formoterol BAI assessment was replaced with the ability to trigger the inhaler. The order of assessments at a combined Visit 1 and 2 was clarified. Inconsistency in regards to the follow-up period was corrected The SAE reporting email address was changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported