Clinical trial results:
A 12 Week, Randomized, Open-Label, Parallel Group Study to Evaluate the Mastery of Inhaler Technique for Budesonide Formoterol (BF) Spiromax(160/4.5 and 320/9 mcg) as Compared to SYMBICORT® TURBOHALER® (200/6 and 400/12 mcg) as Treatment for Adult Patients with Asthma (the Easy Low Instruction Over Time [ELIOT] Study)

Summary

EudraCT number	2013-004630-14
Trial protocol	GB
Global end of trial date	13 March 2015

Results information

Result version number	v1 (current)
This version publication date	13 May 2017
First version publication date	13 May 2017

Trial information

Trial identification

Sponsor protocol code	BFS-AS-40035

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02062463
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	41 Moores Road, Frazer, Pennsylvania, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 215 591 3000,
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 215 591 3000,

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	15 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a 2-stage study. The primary objectives of the study are as follows:

•Stage 1: to determine the proportion of subjects achieving device mastery by the end of Step 3 of a 6-step standardized device training protocol for empty SPIROMAX is superior to empty TURBOHALER devices. Device mastery is defined as absence of nurse-observed errors.

•Stage 2: to determine whether the proportion of subjects maintaining device mastery, in subjects receiving inhaled corticosteroids/long-acting beta agonists (ICS/LABA) via BF SPIROMAX, is superior to ICS/LABA received via SYMBICORT TURBOHALER. Maintenance of device mastery is defined as absence of nurse-observed errors after 12 weeks of device use.

Protection of trial subjects:

For adult subjects, written informed consent signed and dated by the subject before conducting any study-related procedures; for minor subjects, written informed consent signed and dated by the parent/legal guardian and written assent signed and dated by the subject before conducting any study related procedure.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	28 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: 540
Worldwide total number of subjects	540
EEA total number of subjects	540

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)	390
From 65 to 84 years	150
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 540 patients with asthma were screened for enrollment into stage 1 of this study and 485 were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Empty SPIROMAX Followed by Empty TURBOHALER

Arm description:

Subjects were randomly assigned to training with empty SPIROMAX followed by empty SYMBICORT TURBOHALER devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.

Arm type	Empty device
Investigational medicinal product name	Empty Budesonide/Formoterol (BF) SPIROMAX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Subjects were educated on the device using empty training devices containing no active drug and no excipients.

Investigational medicinal product name	Empty SYMBICORT TURBOHALER
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Subjects were educated on the device using empty training devices containing no active drug excipients.

Arm title	Empty TURBOHALER Followed by Empty SPIROMAX

Arm description:

Subjects were randomly assigned to training with empty SYMBICORT TURBOHALER followed by empty SPIROMAX devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.

Arm type	Empty device
Investigational medicinal product name	Empty SYMBICORT TURBOHALER
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Subjects were educated on the device using empty training devices containing no active drug excipients.

Investigational medicinal product name	Empty Budesonide/Formoterol (BF) SPIROMAX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Subjects were educated on the device using empty training devices containing no active drug and no excipients.

Number of subjects in period 1	Empty SPIROMAX Followed by Empty TURBOHALER	Empty TURBOHALER Followed by Empty SPIROMAX
Started	243	242
Completed	240	241
Not completed	3	1
Consent withdrawn by subject	1	-
Reason not collected per protocol	2	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BF SPIROMAX

Arm description:

ICS/LABA via the BF SPIROMAX device for 12 weeks of therapy.

Arm type	Experimental
Investigational medicinal product name	Budesonide/Formoterol (BF) SPIROMAX
Investigational medicinal product code	
Other name	budesonide/formoterol fumarate dihydrate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

The doses in stage 2 were equivalent to that received via the subject's current device at baseline. Subjects who had had been receiving 800 to 1000 µg beclometasone-equivalent ICS per day were randomly assigned to receive 2 doses of budesonide/formoterol twice daily using the BF SPIROMAX 160/4.5 µg device. Subjects who had been receiving 1600 to 2000 µg beclometasone-equivalent ICS per day were randomly assigned to receive 2 doses of budesonide/formoterol twice daily using the BF SPIROMAX 320/9 µg device.

Arm title	SYMBICORT TURBOHALER

Arm description:

ICS/LABA via the SYMBICORT TURBOHALER device for 12 weeks of therapy.

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:

The doses in stage 2 were equivalent to that received via the subject's current device at baseline. Subjects who had had been receiving 800 to 1000 µg beclometasone-equivalent ICS per day were randomly assigned to receive 2 doses of budesonide/formoterol twice daily using the SYMBICORT TURBOHALER 200/6 µg device. Subjects who had been receiving 1600 to 2000 µg beclometasone equivalent ICS per day were randomly assigned to receive 2 doses of budesonide/formoterol twice daily using the SYMBICORT TURBOHALER 400/12 µg device.

Number of subjects in period 2	BF SPIROMAX	SYMBICORT TURBOHALER
Started	197	197
Completed	144	141
Not completed	53	56
Consent withdrawn by subject	15	10
Not specified	3	1
Adverse event	12	20
Non-compliance	-	1
Lost to follow-up	20	20
Lack of efficacy	3	4

Baseline characteristics

Reporting groups[1]	
Reporting group title	Empty SPIROMAX Followed by Empty TURBOHALER

Reporting group description:

Subjects were randomly assigned to training with empty SPIROMAX followed by empty SYMBICORT TURBOHALER devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.

Reporting group title	Empty TURBOHALER Followed by Empty SPIROMAX

Reporting group description:

Subjects were randomly assigned to training with empty SYMBICORT TURBOHALER followed by empty SPIROMAX devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.

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: 485 of the enrolled subjects were randomized and entered Stage 1.

Reporting group values	Empty SPIROMAX Followed by Empty TURBOHALER	Empty TURBOHALER Followed by Empty SPIROMAX	Total
Number of subjects	243	242	485
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.4	53.1	
standard deviation	± 13.8	± 14.2	-
Gender categorical Units: Subjects			
Female	152	134	286
Male	91	108	199

End points

End points reporting groups

Reporting group title	Empty SPIROMAX Followed by Empty TURBOHALER
Reporting group description:	
Subjects were randomly assigned to training with empty SPIROMAX followed by empty SYMBICORT TURBOHALER devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.	
Reporting group title	Empty TURBOHALER Followed by Empty SPIROMAX
Reporting group description:	
Subjects were randomly assigned to training with empty SYMBICORT TURBOHALER followed by empty SPIROMAX devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.	
Reporting group title	BF SPIROMAX
Reporting group description:	
ICS/LABA via the BF SPIROMAX device for 12 weeks of therapy.	
Reporting group title	SYMBICORT TURBOHALER
Reporting group description:	
ICS/LABA via the SYMBICORT TURBOHALER device for 12 weeks of therapy.	
Subject analysis set title	Stage 1 Full Analysis Set: Empty SPIROMAX
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects who completed both assessments (so permitting a paired analysis of results).	
Subject analysis set title	Stage 1 Full Analysis Set: Empty TURBOHALER
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects who completed both assessments (so permitting a paired analysis of results).	
Subject analysis set title	Stage 2 Full Analysis Set: BF SPIROMAX
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects who return for assessment of maintenance of inhaler technique at Week 12 using the inhaler (treatment) to which they were randomly assigned (BF SPIROMAX).	
Subject analysis set title	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects who return for assessment of maintenance of inhaler technique at Week 12 using the inhaler (treatment) to which they were randomly assigned (SYMBICORT TURBOHALER).	
Subject analysis set title	Stage 2 Intent-to-treat: BF SPIROMAX
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects taking BF SPIROMAX	
Subject analysis set title	Stage 2 Intent-to-treat: SYMBICORT TURBOHALER
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects taking SYMBICORT TURBOHALER.	

Primary: Stage 1: Number of Subjects Achieving Device Mastery

End point title	Stage 1: Number of Subjects Achieving Device Mastery[1]
End point description:	
Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an	

assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors.

End point type	Primary

End point timeframe:

1 day

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis offered as a PDF attachment.

End point values	Stage 1 Full Analysis Set: Empty SPIROMAX	Stage 1 Full Analysis Set: Empty TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	481	481		
Units: subjects				
Yes	454	418		
No	27	63		

Attachments (see zip file)	Statistical Analysis_Primary Endpoint Stage 1 Device Mastery.

Statistical analyses

No statistical analyses for this end point

Primary: Stage 2: Number of Subjects Maintaining Device Mastery

End point title	Stage 2: Number of Subjects Maintaining Device Mastery

End point description:

Maintenance of device mastery was defined as absence of nurse-observed errors after 12 weeks of device use.

End point type	Primary

End point timeframe:

12 weeks

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	154		
Units: subjects				
Yes	89	82		
No	62	72		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.316 [3]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.98

Notes:

[2] - BF SPIROMAX relative to SYMBICORT TURBOHALER (SYMBICORT TURBOHALER=1.00).

[3] - The p-value for the treatment comparison is based on chi-square; p<0.05 considered statistically significant.

Secondary: Stage 1: Number of Subjects Achieving Device Mastery by Step 1

End point title	Stage 1: Number of Subjects Achieving Device Mastery by Step 1

End point description:

The number of subjects achieving device mastery by Step 1 (no training/intuitive use) of the device training process. Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors.

End point type	Secondary

End point timeframe:

1 day

End point values	Stage 1 Full Analysis Set: Empty SPIROMAX	Stage 1 Full Analysis Set: Empty TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	481	481		
Units: subjects				
Yes	160	55		
No	321	426		

Attachments (see zip file)	Statistical Analysis_Secondary Endpoint Device Mastery by

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 1: Number of Subjects Achieving Device Mastery by Step 2

End point title	Stage 1: Number of Subjects Achieving Device Mastery by Step 2

End point description:

The number of subjects achieving device mastery by Step 2 (patient information leaflet) of the device training process. Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors.

End point type	Secondary

End point timeframe:

1 day

End point values	Stage 1 Full Analysis Set: Empty SPIROMAX	Stage 1 Full Analysis Set: Empty TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	481	481		
Units: subjects				
Yes	386	308		
No	95	173		

Attachments (see zip file)	Statistical Analysis_Secondary Endpoint Device Mastery by

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 1: Number of Steps Required to Achieve Device Mastery

End point title	Stage 1: Number of Steps Required to Achieve Device Mastery

End point description:

Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors.

End point type	Secondary

End point timeframe:

1 day

End point values	Stage 1 Full Analysis Set: Empty SPIROMAX	Stage 1 Full Analysis Set: Empty TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	481	481		
Units: training steps				
median (full range (min-max))	1 (0 to 12)	2 (0 to 15)		

Attachments (see zip file)	Statistical Analysis_Secondary Endpoint Number of Steps

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 1: Number of Health Care Professional-Observed Errors

End point title	Stage 1: Number of Health Care Professional-Observed Errors

End point description:

Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors.

End point type	Secondary

End point timeframe:

1 day

End point values	Stage 1 Full Analysis Set: Empty SPIROMAX	Stage 1 Full Analysis Set: Empty TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	481	481		
Units: errors				
arithmetic mean (standard deviation)	1.91 (± 0.89)	2.36 (± 0.92)		

Attachments (see zip file)	Statistical Analysis_Secondary Endpoint Number of HCP-

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 1: Subject Preference for the Device

End point title	Stage 1: Subject Preference for the Device

End point description:

Total Patient Satisfaction and Preference Questionnaire (PASAPQ) score. The PASAPQ is a multi-item

measure of respiratory inhalation device satisfaction and preference designed to be easy to understand and administer to asthma and COPD patients (Kozma et al 2005). The PASAPQ is a two-part questionnaire. Part I consists of 14 questions, the first 13 generating the Performance, Convenience and Total Score domains, and a standalone question for Overall Satisfaction. Part II consists of standalone questions concerning a subject's device preference and willingness to continue use.

End point type	Secondary

End point timeframe:

1 day

End point values	Stage 1 Full Analysis Set: Empty SPIROMAX	Stage 1 Full Analysis Set: Empty TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	477[4]	477[5]		
Units: units on a scale				
median (full range (min-max))	89.8 (18.37 to 100)	85.71 (14.29 to 100)		

Notes:

[4] - subjects with an assessment

[5] - subjects with an assessment

Attachments (see zip file)	Statistical Analysis_Secondary Endpoint Subject Preference for

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Total Number of Observed Errors

End point title	Stage 2: Total Number of Observed Errors

End point description:

The total number of observed errors (as observed by health care providers and technology [Vitalograph™ pneumotrac spirometer]).

End point type	Secondary

End point timeframe:

12 weeks

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	154		
Units: observed errors				
arithmetic mean (standard deviation)	0.5 (± 0.68)	0.82 (± 1.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	rate ratio
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.84

Notes:

[6] - BF SPIROMAX relative to SYMBICORT TURBOHALER (SYMBICORT TURBOHALER=1.00). Negative binomial regression was used.

Secondary: Stage 2: Total Number of Technology-Observed Errors

End point title	Stage 2: Total Number of Technology-Observed Errors
End point description:	
The total number of technology-observed errors (by Vitalograph™ pneumotrac spirometer).	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	154		
Units: errors				
arithmetic mean (standard deviation)	0.01 (± 0.08)	0.01 (± 0.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Total Number of Handling Errors

End point title	Stage 2: Total Number of Handling Errors
End point description:	
The total number of observed handling errors (as observed by health care providers).	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	154		
Units: errors				
arithmetic mean (standard deviation)	0.5 (± 0.67)	0.81 (± 1.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[7]
Parameter estimate	rate ratio
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.84

Notes:

[7] - Negative binomial regression model was used.

Secondary: Stage 2: Difference in Handling Errors from Stage 1 to Stage 2 (12 weeks)

End point title	Stage 2: Difference in Handling Errors from Stage 1 to Stage 2 (12 weeks)

End point description:

The difference in number of handling errors identified following training using patient device information leaflet at Stage 1 and after 12 weeks of treatment (end of Stage 2).

End point type	Secondary

End point timeframe:

12 weeks

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	154		
Units: errors				
arithmetic mean (standard deviation)	-0.95 (± 1.72)	-2.01 (± 2.52)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[8]
Parameter estimate	rate ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.54

Notes:

[8] - Negative binomial regression model was used.

Secondary: Stage 2: Treatment Adherence

End point title	Stage 2: Treatment Adherence
End point description:	
Percentage of treatment adherence by subject as assessed by device dose counters.	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	154		
Units: subjects				
</= 50% adherence	60	61		
51% to 70% adherence	19	16		
71% to 99% adherence	70	71		
100% adherence	2	6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.523 [9]
Method	Chi-squared

Notes:

[9] - $p < 0.05$ is considered statistically significant.

Secondary: Stage 2: Change in 6-item Asthma Control Questionnaire (ACQ) From Baseline to 4, 8, and 12 Weeks

End point title	Stage 2: Change in 6-item Asthma Control Questionnaire (ACQ) From Baseline to 4, 8, and 12 Weeks

End point description:

Change in the 6-item ACQ from Baseline to 4, 8, and 12 weeks. The ACQ is a 7-item, validated tool for assessing asthma control (Juniper et al 1999). Thinking about their asthma for the last 7 days,subjects were asked to evaluate their asthma against 5 symptom items and a rescue bronchodilator use question using a 7-point scale (0=no impairment and 6=maximum impairment). Spirometry data were used to grade the percent predicted forced expiratory volume in 1 second (FEV1) on a 7-point scale (0 to 6). The score is the mean of the first 6 questions (excluding the FEV1 question), generating a value from 0 (totally controlled) to 6 (severely uncontrolled). A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, 4, 8, and 12 weeks

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151[10]	154[11]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 4; n=142, 140	-0.22 (± 0.83)	-0.33 (± 0.81)		
Week 8; n=140, 143	-0.2 (± 0.98)	-0.3 (± 1.04)		
Week 12; n=137, 147	-0.22 (± 0.95)	-0.36 (± 1.05)		

Notes:

[10] - n=number of subjects with an assessment at Baseline and given time point

[11] - n=number of subjects with an assessment at Baseline and given time point

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Week 4	
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	treatment difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.3

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Week 8	
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	treatment difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.33

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Week 12	
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	treatment difference
Point estimate	0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.37

Secondary: Stage 2: Change in the 7-item ACQ From Baseline to Week 12

End point title	Stage 2: Change in the 7-item ACQ From Baseline to Week 12

End point description:

Change in 7-item ACQ (including FEV1 question) from baseline to Week 12. The ACQ is a 7-item, validated tool for assessing asthma control (Juniper et al 1999). Thinking about their asthma for the last 7 days, subjects were asked to evaluate their asthma against 5 symptom items and a rescue bronchodilator use question using a 7-point scale (0=no impairment and 6=maximum impairment). Spirometry data were used to grade the percent predicted FEV1 on a 7-point scale (0 to 6). The ACQ score is the mean of the 7 questions, generating a value from 0 (totally controlled) to 6 (severely uncontrolled). A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	145[12]	149[13]		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.2 (± 0.78)	-0.31 (± 0.92)		

Notes:

[12] - subjects with an assessment at Baseline and Week 12

[13] - subjects with an assessment at Baseline and Week 12

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	treatment difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.3

Secondary: Stage 2: Time to First Treatment Failure

End point title	Stage 2: Time to First Treatment Failure

End point description:

The time to treatment failure, defined as change of asthma treatment or treatment for an asthma exacerbation or lower respiratory tract infection.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151[14]	154[15]		
Units: days				
arithmetic mean (standard deviation)	76.38 (± 21.42)	73.95 (± 24.27)		

Notes:

[14] - subjects with treatment failure=29

[15] - subjects with treatment failure=40

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.159 [16]
Method	Log-rank (Mantel-Cox)

Notes:

[16] - $p < 0.05$ is considered statistically significant.

Secondary: Stage 2: Number of Severe Asthma Exacerbations

End point title	Stage 2: Number of Severe Asthma Exacerbations

End point description:

Number of severe asthma exacerbations, defined as a hospitalization or emergency room attendance for asthma, or an acute course of oral corticosteroids.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Stage 2 Intent-to-treat: BF SPIROMAX	Stage 2 Intent-to-treat: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	197		
Units: subjects				
No exacerbations	178	176		
One exacerbation	18	20		
Two exacerbations	1	1		
Three or more exacerbaions	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Impact of Maintaining Device Mastery on Time to Treatment Failure

End point title	Stage 2: Impact of Maintaining Device Mastery on Time to Treatment Failure

End point description:

The impact of maintaining device mastery on time to treatment failure (defined as change of asthma treatment or treatment for an asthma exacerbation or lower respiratory tract infection) was assessed by comparing the time to treatment failure for subjects with and without device mastery. Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device.

End point type	Secondary

End point timeframe:

Week 12

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151[17]	154[18]		
Units: days				
arithmetic mean (standard deviation)				
Device mastery=yes; n=89, 82	72.99 (± 22.38)	75.93 (± 22.59)		
Device mastery=no; n=62, 72	81.24 (± 19.11)	71.69 (± 26.03)		

Notes:

[17] - n=subjects with or without device mastery

[18] - n=subjects with or without device mastery

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[19]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.38

Notes:

[19] - Cox Regression with device and device mastery as covariates.

Secondary: Stage 2: Impact of Maintaining Device Mastery on Asthma Control

End point title	Stage 2: Impact of Maintaining Device Mastery on Asthma Control

End point description:

The impact of maintaining device mastery on asthma control was assessed by comparing the 7-item ACQ scores for subjects with and without device mastery. The ACQ is a 7-item, validated tool for assessing asthma control (Juniper et al 1999). Thinking about their asthma for the last 7 days, subjects were asked to evaluate their asthma against 5 symptom items and a rescue bronchodilator use question using a 7-point scale (0=no impairment and 6=maximum impairment). Spirometry data were used to grade the percent predicted FEV1 on a 7-point scale (0 to 6). The ACQ score is the mean of the 7 questions, generating a value from 0 (totally controlled) to 6 (severely uncontrolled). Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151[20]	154[21]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Device mastery=yes; n=85, 79	1.25 (± 1.05)	1.35 (± 0.95)		
Device mastery=no; n=60, 70	1.46 (± 0.97)	1.37 (± 0.97)		

Notes:

[20] - n=subjects with or without device mastery

[21] - n=subjects with or without device mastery

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	2.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.64
upper limit	7.71

Secondary: Stage 2: Percentage of Patients Maintaining Device Mastery Relating to Dose Preparation Errors

End point title	Stage 2: Percentage of Patients Maintaining Device Mastery Relating to Dose Preparation Errors

End point description:

Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. This analysis is limited to errors affecting dose preparation, such as not twisting the base as far as possible, until it clicks and not turning it back to its original position.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Stage 2 Full Analysis Set: BF SPIROMAX	Stage 2 Full Analysis Set: SYMBICORT TURBOHALER		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	154		
Units: percentage of participants				
number (not applicable)				
Yes: maintained device mastery	76.2	69.5		
No: did not maintain device mastery	23.8	30.5		

Statistical analyses

Statistical analysis title	Mastery: Dose Prep Errors Only
Comparison groups	Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	2.34

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Through Week 12	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	BF SPIROMAX
Reporting group description:	
Inhaled corticosteroid/long-acting β2-agonist via the BF SPIROMAX device for 12 weeks of therapy.	
Reporting group title	SYMBICORT TURBOHALER
Reporting group description:	
Inhaled corticosteroid/long-acting β2-agonist via the SYMBICORT TURBOHALER device for 12 weeks of therapy.	

Serious adverse events	BF SPIROMAX	SYMBICORT TURBOHALER	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 197 (2.03%)	8 / 197 (4.06%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	0 / 197 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 197 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 197 (0.51%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	0 / 197 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 197 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 197 (0.00%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian mass			
subjects affected / exposed	0 / 197 (0.00%)	1 / 197 (0.51%)	
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			
Asthma			
subjects affected / exposed	2 / 197 (1.02%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 197 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 197 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			

subjects affected / exposed	1 / 197 (0.51%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 197 (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	BF SPIROMAX	SYMBICORT TURBOHALER	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 197 (14.21%)	39 / 197 (19.80%)	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 197 (5.58%)	12 / 197 (6.09%)	
occurrences (all)	11	12	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	16 / 197 (8.12%)	29 / 197 (14.72%)	
occurrences (all)	16	29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2014	The following major procedural changes (not all-inclusive) were made to the protocol: • removal of allowance for subject rescreening • changing the ACQ and PASAPQ from verbally administered to written completion by the subject
24 March 2014	The following major procedural changes (not all-inclusive) were made to the protocol: • amended the errata associated with BF SPIROMAX devices resulting from recently available stability data • removed the collection of peripheral blood for eosinophil assessment as a procedure

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported