Clinical trial results:
A 12-Week Efficacy and Safety Evaluation of Budesonide/Formoterol SPIROMAX® 160/4.5 mcg Inhalation Powder Versus SYMBICORT® TURBOHALER® 200/6 mcg in Adult and Adolescent Patients with Persistent Asthma

Summary

EudraCT number	2013-000081-11
Trial protocol	HU AT DE BE IT SE CZ FI ES PL NL DK
Global end of trial date	20 March 2014

Results information

Result version number	v1 (current)
This version publication date	27 May 2016
First version publication date	27 May 2016
Summary attachment (see zip file)	Nonserious AEs During Run-in Period (Nonserious AEs During Run-in Period.docx)

Trial information

Trial identification

Sponsor protocol code	BFS-AS-306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01803555
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	41 Moores Road, Frazer, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 215 591 3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 215 591 3000, ustevatrials@tevapharm.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to establish the non-inferiority of BF SPIROMAX 160/4.5 mcg with that of SYMBICORT TURBOHALER 200/6 mcg administered twice daily in patients 12 years of age and older with persistent asthma, as assessed by the change from baseline in average daily trough (predose and pre-rescue bronchodilator) morning (AM) peak expiratory flow (PEF) rate over a 12-week treatment period. The secondary objectives of the study were to evaluate subject preference and ease of use of the BF SPIROMAX 160/4.5 mcg device compared to SYMBICORT TURBOHALER 200/6 mcg.

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.

Stopping criteria for worsening asthma were designed to assure subject safety. The study drug was stopped and the patient was withdrawn from the study if any of the criteria listed below were met:
• clinic forced expiratory volume (FEV1) fell below the FEV1 stability limit value calculated at Visit 2
• during the 7 days immediately preceding any treatment visits (Visits 2 to 5), if the patient experienced:
- more than 3 days in which the peak expiratory flow (PEF) fell below the PEF stability limit calculated at visit 2
- more than 2 days in which ≥ 12 inhalations/day of albuterol/salbutamol were used
- more than 1 night with awakening due to asthma symptoms requiring use of rescue albuterol/salbutamol
- clinical asthma exacerbation, defined as worsening asthma requiring any treatment other than study drug or rescue albuterol/salbutamol, including the use of systemic corticosteroids and/or emergency room visit or hospitalization.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	04 July 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	Netherlands: 12
Country: Number of subjects enrolled	Poland: 236
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Sweden: 10

Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 23
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 105
Country: Number of subjects enrolled	Hungary: 85
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Russian Federation: 71
Worldwide total number of subjects	671
EEA total number of subjects	582

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)	38
Adults (18-64 years)	539
From 65 to 84 years	94
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 725 subjects with persistent asthma were screened for enrollment into this study. Of these, 671 subjects at 112 study centers worldwide met entry criteria and were considered to be eligible for enrollment into the run-in period of the study.

Pre-assignment

Screening details:

During the run-in period, all subjects continued to use their current daily asthma medications at fixed doses. The rescue medication (albuterol/salbutamol) dispensed at visit 1 was provided by TEVA and permitted for symptomatic relief of asthma symptoms during the run-in period and replaced the subject's current rescue therapy.

Pre-assignment period milestones

Number of subjects started	671
Number of subjects completed	605

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion criteria not met: 5
Reason: Number of subjects	Consent withdrawn by subject: 5
Reason: Number of subjects	Randomization criteria not met: 2
Reason: Number of subjects	Adverse event: 1
Reason: Number of subjects	Lost to follow-up: 1
Reason: Number of subjects	Not specified: 52

Period 1

Period 1 title	Randomized Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

At the baseline visit (Visit 2; end of the run-in period), subjects meeting the eligibility criteria were randomized to the 84-day treatment period. In the event of an emergency, if it was necessary to know what treatment a specific patient received, the investigator was allowed to determine the patient's treatment with or without consulting the sponsor, depending on the nature and severity of the emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	BF SPIROMAX

Arm description:

2 inhalations of BF SPIROMAX at a dosage of 160/4.5 mcg (budesonide/formoterol fumarate dihydrate 160/4.5 mcg) and 2 inhalations of placebo SYMBICORT administered twice daily (AM and PM) during the 12-week treatment period.

Arm type	Experimental

Investigational medicinal product name	Budesonide/Formoterol (BF) SPIROMAX (budesonide/formoterol fumarate dihydrate 160/4.5 mcg)
Investigational medicinal product code	BF Spiromax
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

During the treatment period (Visit 2 through Visit 5), subjects administered the double-blind study medication twice daily. All subjects continued albuterol/salbutamol for use on an as needed basis for the relief of asthma symptoms throughout the treatment period.

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

Dosage and administration details:

During the treatment period (Visit 2 through Visit 5), subjects administered the double-blind study medication twice daily. All subjects continued albuterol/salbutamol for use on an as needed basis for the relief of asthma symptoms throughout the treatment period.

Arm title	SYMBICORT TURBOHALER

Arm description:

2 inhalations of SYMBICORT TURBOHALER at a dosage of 200/6 mcg and 2 inhalations of placebo SPIROMAX administered twice daily (AM and PM) during the 12-week treatment period.

Arm type	Active comparator
Investigational medicinal product name	SYMBICORT® TURBOHALER® 200/6 mcg inhalation powder
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

During the treatment period (Visit 2 through Visit 5), subjects administered the double-blind study medication twice daily. All subjects continued albuterol/salbutamol for use on an as needed basis for the relief of asthma symptoms throughout the treatment period.

Investigational medicinal product name	Placebo SPIROMAX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

During the treatment period (Visit 2 through Visit 5), subjects administered the double-blind study medication twice daily. All subjects continued albuterol/salbutamol for use on an as needed basis for the relief of asthma symptoms throughout the treatment period.

Number of subjects in period 1[1]	BF SPIROMAX	SYMBICORT TURBOHALER
Started	303	302
Completed	290	284
Not completed	13	18
Consent withdrawn by subject	3	3
Not specified	3	5

Adverse event	3	2
Lost to follow-up	-	2
Noncompliance	1	1
Protocol deviation	3	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects accounted for in the Run-in period (ie, Pre-assignment period; n=671) equals the worldwide number enrolled in the trial.

Baseline characteristics

Reporting groups	
Reporting group title	BF SPIROMAX
Reporting group description:	
2 inhalations of BF SPIROMAX at a dosage of 160/4.5 mcg (budesonide/formoterol fumarate dihydrate 160/4.5 mcg) and 2 inhalations of placebo SYMBICORT administered twice daily (AM and PM) during the 12-week treatment period.	
Reporting group title	SYMBICORT TURBOHALER
Reporting group description:	
2 inhalations of SYMBICORT TURBOHALER at a dosage of 200/6 mcg and 2 inhalations of placebo SPIROMAX administered twice daily (AM and PM) during the 12-week treatment period.	

Reporting group values	BF SPIROMAX	SYMBICORT TURBOHALER	Total
Number of subjects	303	302	605
Age categorical Units: Subjects			
Adolescents (12-17 years)	18	20	38
Adults (18-64 years)	242	242	484
From 65-84 years	43	40	83
Age continuous Units: years			
arithmetic mean	48.1	46.9	
standard deviation	± 16.24	± 16.89	-
Gender categorical Units: Subjects			
Female	172	161	333
Male	131	141	272

End points

End points reporting groups

Reporting group title	BF SPIROMAX

Reporting group description:

2 inhalations of BF SPIROMAX at a dosage of 160/4.5 mcg (budesonide/formoterol fumarate dihydrate 160/4.5 mcg) and 2 inhalations of placebo SYMBICORT administered twice daily (AM and PM) during the 12-week treatment period.

Reporting group title	SYMBICORT TURBOHALER

Reporting group description:

2 inhalations of SYMBICORT TURBOHALER at a dosage of 200/6 mcg and 2 inhalations of placebo SPIROMAX administered twice daily (AM and PM) during the 12-week treatment period.

Subject analysis set title	BF SPIROMAX (per protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in the BF SPIROMAX treatment arm included in the per-protocol (PP) population. The PP population includes all data from randomized subjects obtained before experiencing major protocol violations, which were determined before unblinding.

Subject analysis set title	SYMBICORT TURBOHALER (per protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in the SYMBICORT TURBOHALER treatment arm included in the per-protocol (PP) population. The PP population includes all data from randomized subjects obtained before experiencing major protocol violations, which were determined before unblinding.

Primary: Change in Weekly Average of Daily Trough Morning (AM) Peak Expiratory Flow (PEF) From Baseline Over the 12-week Treatment Period

End point title	Change in Weekly Average of Daily Trough Morning (AM) Peak Expiratory Flow (PEF) From Baseline Over the 12-week Treatment Period

End point description:

PEF was determined twice daily, in the AM and in the evening (PM), before administration of study or rescue medications during the run-in period and throughout the 12-week double-blind treatment period. A handheld electronic peak flow meter was provided to subjects at the screening visit (Visit 1) and used to determine AM and PM PEFs throughout the course of the study. The highest value of triplicate measurements obtained in the AM and PM was to be recorded by subjects into a paper diary.

End point type	Primary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication) through Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	290	284		
Units: L/min				
least squares mean (standard error)	18.839 (± 2.754)	21.796 (± 2.745)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Performed using a repeated measures mixed model with effects due to baseline weekly average of daily trough AM PEF, gender, age, treatment, time, and treatment-by-time interaction. It is noted that missing data were not implicitly imputed in the repeated measures mixed model analysis; however, all non-missing data were used within the analysis to estimate the time-averaged difference between treatment groups over 12 weeks.

Comparison groups	SYMBICORT TURBOHALER (per protocol) v BF SPIROMAX (per protocol)
Number of subjects included in analysis	574
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.3387 [2]
Method	repeated measures mixed model
Parameter estimate	least squares mean
Point estimate	-2.957
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.02
upper limit	3.11

Notes:

[1] - The non-inferiority of BF SPIROMAX 160/4.5 mcg to SYMBICORT TURBOHALER 200/6 mcg was demonstrated if the lower limit of the 2 sided 95% CI for the treatment difference is greater than –15 L/min.

[2] - No explicit structure was assumed for the covariance among the repeated measures. However, in case there was a convergence problem with the unstructured covariance, then a compound symmetry or AR(1) covariance structure was assumed.

Secondary: Change in Weekly Average of Daily Trough Evening (PM) PEF From Baseline Over the 12-week Treatment Period

End point title	Change in Weekly Average of Daily Trough Evening (PM) PEF From Baseline Over the 12-week Treatment Period

End point description:

PEF was determined twice daily, in the AM and in the PM, before administration of study or rescue medications during the run-in period and throughout the 12-week double-blind treatment period. A handheld electronic peak flow meter was provided to subjects at the screening visit (Visit 1) and used to determine AM and PM PEFs throughout the course of the study. The highest value of triplicate measurements obtained in the AM and PM was to be recorded by subjects into a paper diary.

End point type	Secondary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication) through Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	290	284		
Units: L/Min				
least squares mean (standard error)	18.661 (± 2.631)	21.74 (± 2.622)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Performed using a repeated measures mixed model with effects due to baseline weekly average of daily trough PM PEF, gender, age, treatment, time, and treatment-by-time interaction. It is noted that missing data were not implicitly imputed in the repeated measures mixed model analysis; however, all non-missing data were used within the analysis to estimate the time-averaged difference between treatment groups over 12 weeks.

Comparison groups	SYMBICORT TURBOHALER (per protocol) v BF SPIROMAX (per protocol)
Number of subjects included in analysis	574
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293 [3]
Method	repeated measures mixed model
Parameter estimate	least squares mean
Point estimate	-3.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.82
upper limit	2.67

Notes:

[3] - No explicit structure was assumed for the covariance among the repeated measures. However, in case there was a convergence problem with the unstructured covariance, then a compound symmetry or AR(1) covariance structure was assumed.

Secondary: Change From Baseline Over the 12-week Treatment Period in the Percentage of Symptom-free 24-hour Periods

End point title	Change From Baseline Over the 12-week Treatment Period in the Percentage of Symptom-free 24-hour Periods

End point description:

End point type	Secondary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication) through Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	290	284		
Units: percentage of symptom-free 24-hr periods				

median (full range (min-max))	20.5 (-94 to 100)	27.8 (-93.3 to 100)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BF SPIROMAX (per protocol) v SYMBICORT TURBOHALER (per protocol)
Number of subjects included in analysis	574
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3082
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.97
upper limit	1.19

Secondary: Change From Baseline Over the 12-Week Treatment Period in the Percentage of Rescue-Free 24-Hour Periods

End point title	Change From Baseline Over the 12-Week Treatment Period in the Percentage of Rescue-Free 24-Hour Periods

End point description:

End point type	Secondary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication) through Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	290	284		
Units: percentage of rescue-free 24-hr periods				
median (full range (min-max))	32.7 (-49.5 to 100)	35.7 (-73.5 to 100)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BF SPIROMAX (per protocol) v SYMBICORT TURBOHALER (per protocol)
Number of subjects included in analysis	574
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.23
upper limit	2.38

Secondary: Change From Baseline in Trough Forced Expiratory Volume in 1 Second (FEV1) Over the 12-Week Treatment Period

End point title	Change From Baseline in Trough Forced Expiratory Volume in 1 Second (FEV1) Over the 12-Week Treatment Period

End point description:

Change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV1 over the 12-week treatment period

End point type	Secondary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication) through Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	283[4]	280[5]		
Units: Liters				
least squares mean (standard error)	0.325 (± 0.025)	0.318 (± 0.025)		

Notes:

[4] - subjects who contributed at least once to the analysis

[5] - subjects who contributed at least once to the analysis

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BF SPIROMAX (per protocol) v SYMBICORT TURBOHALER (per protocol)

Number of subjects included in analysis	563
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7661 [6]
Method	repeated measures mixed model
Parameter estimate	least squares mean
Point estimate	0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.06

Notes:

[6] - analyzed using a repeated measures mixed model with effects due to baseline trough FEV1, gender, age, visit, treatment, and visit by treatment interaction

Secondary: Change From Baseline in Patient Satisfaction and Preference Questionnaire for Inhalation Devices (PASAPQ) Overall Satisfaction Scores Over the 12-Week Treatment Period

End point title	Change From Baseline in Patient Satisfaction and Preference Questionnaire for Inhalation Devices (PASAPQ) Overall Satisfaction Scores Over the 12-Week Treatment Period

End point description:

Change from baseline in PASAPQ total satisfaction score (Part I of PASAPQ). The PASAPQ is a multi-item measure of inhalation device satisfaction and preference designed specifically for patients with asthma and chronic obstructive pulmonary disease. The PASAPQ includes a total of 14 device satisfaction items, including an overall satisfaction item, each rated on a 7-point response scale from "very dissatisfied" (1) to "very satisfied" (7). Each of the satisfaction items was asked twice, once for each study device. The mean of the 14 satisfaction items, including the overall satisfaction item, form a total satisfaction score.

End point type	Secondary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication) through Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	276[7]	266[8]		
Units: units on a scale				
least squares mean (standard error)	0.181 (± 0.082)	0.04 (± 0.082)		

Notes:

[7] - subjects who contributed at least once to the analysis

[8] - subjects who contributed at least once to the analysis

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BF SPIROMAX (per protocol) v SYMBICORT TURBOHALER (per protocol)

Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1016 [9]
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	0.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.31

Notes:

[9] - Analyzed using an analysis of covariance (ANCOVA) model with effects due to baseline score, gender, age, and treatment, imputing missing data via last observation carried forward. Both original scale and transformed scale were used.

Secondary: Change From Baseline in PASAPQ Performance and Convenience Domain Scores Over the 12-Week Treatment Period

End point title	Change From Baseline in PASAPQ Performance and Convenience Domain Scores Over the 12-Week Treatment Period

End point description:

Change from baseline in PASAPQ domain scores of performance (7 items) and convenience (6 items; Part I). The PASAPQ is a multi-item measure of inhalation device satisfaction and preference designed specifically for patients with asthma and chronic obstructive pulmonary disease. The PASAPQ The PASAPQ has 2 subscale scores: performance (7 items) and convenience (6 items), each rated on a 7-point response scale from "very dissatisfied" (1) to "very satisfied" (7). Each of the items was asked twice, once for each study device.

End point type	Secondary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication) through Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	276[10]	266[11]		
Units: units on a scale				
least squares mean (standard error)				
Change in performance domain scores	0.212 (± 0.065)	0.012 (± 0.066)		
Change in convenience domain scores	0.042 (± 0.06)	0.118 (± 0.06)		

Notes:

[10] - subjects who contributed at least once to the analysis

[11] - subjects who contributed at least once to the analysis

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Performance domain score difference

Comparison groups	BF SPIROMAX (per protocol) v SYMBICORT TURBOHALER (per protocol)
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038 [12]
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.34

Notes:

[12] - Analyzed using an ANCOVA model with effects due to baseline score, gender, age, and treatment, imputing missing data via last observation carried forward. Both original scale and transformed scale were used.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Convenience domain score difference

Comparison groups	BF SPIROMAX (per protocol) v SYMBICORT TURBOHALER (per protocol)
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2206 [13]
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.05

Notes:

[13] - Analyzed using an ANCOVA model with effects due to baseline score, gender, age, and treatment, imputing missing data via last observation carried forward. Both original scale and transformed scale were used.

Secondary: Change From Baseline in PASAPQ Device Preference Scores Over the 12-Week Treatment Period

End point title	Change From Baseline in PASAPQ Device Preference Scores Over the 12-Week Treatment Period

End point description:

Number of subjects with a change from baseline (BL) in device preference, using the PASAPQ device preference score (Part II). The PASAPQ is a multi-item measure of inhalation device satisfaction and preference designed specifically for patients with asthma and chronic obstructive pulmonary disease. The PASAPQ includes a device preference item, which is rated using a 3-level categorical response scale: "I prefer inhaler 1," "I prefer inhaler 2," "no preference." Inhaler 1 was used for BF SPIROMAX and its placebo. Inhaler 2 was used for SYMBICORT TURBOHALER and its placebo.

End point type	Secondary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication) through Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	274[14]	263[15]		
Units: subjects				
BL no preference / Week 12 no preference	26	26		
BL no preference / Week 12 prefer inhaler 1	14	26		
BL no preference / Week 12 prefer inhaler 2	9	14		
BL prefer inhaler 1 / Week 12 no preference	38	33		
BL prefer inhaler 1 / Week 12 prefer inhaler 1	96	88		
BL prefer inhaler 1 / Week 12 prefer inhaler 2	31	18		
BL prefer inhaler 2 / Week 12 no preference	18	14		
BL prefer inhaler 2 / Week 12 prefer inhaler 1	17	15		
BL prefer inhaler 2 / Week 12 prefer inhaler 2	25	29		

Notes:

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BF SPIROMAX (per protocol) v SYMBICORT TURBOHALER (per protocol)
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2011
Method	Cochran-Mantel-Haenszel

Secondary: Change From Baseline in PASAPQ Willingness to Continue Using the Device Scores Over the 12-Week Treatment Period

End point title	Change From Baseline in PASAPQ Willingness to Continue Using the Device Scores Over the 12-Week Treatment Period

End point description:

Change from baseline in PASAPQ willingness to continue using the device score (Part II) at Week 12. The PASAPQ is a multi-item measure of inhalation device satisfaction and preference designed specifically for patients with asthma and chronic obstructive pulmonary disease. The PASAPQ includes an item on willingness to continue using the device in the future, which is rated using a numerical rating scale from 0 to 100, once for each study device.

End point type	Secondary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication) through Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272[16]	261[17]		
Units: units on a scale				
least squares mean (standard error)	3.65 (± 2.047)	-3.951 (± 2.066)		

Notes:

[16] - subjects who contributed at least once to the analysis

[17] - subjects who contributed at least once to the analysis

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BF SPIROMAX (per protocol) v SYMBICORT TURBOHALER (per protocol)
Number of subjects included in analysis	533
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [18]
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.33
upper limit	11.87

Notes:

[18] - Analyzed using an ANCOVA model with effects due to baseline score, gender, age, and treatment, imputing missing data via LOCF.

Secondary: Change From Baseline in Overall Inhaler Quickness Satisfaction at Week 12

End point title	Change From Baseline in Overall Inhaler Quickness Satisfaction at Week 12

End point description:

Participants responded to the overall device quickness satisfaction question "How satisfied are you with the overall quickness of using your inhaler?" at Baseline and Week 12. Answers were: very dissatisfied, dissatisfied, somewhat dissatisfied, neither satisfied nor dissatisfied, somewhat satisfied, satisfied, and very satisfied. Change from baseline in PASAPQ total satisfaction score (Part I of PASAPQ). The PASAPQ is a multi-item measure of inhalation device satisfaction and preference designed specifically for patients with asthma and chronic obstructive pulmonary disease. The PASAPQ includes a total of 14 device satisfaction items, including an overall quickness satisfaction item, each rated on a 7-point response scale from “very dissatisfied” (1) to “very satisfied” (7). Each of the satisfaction items was asked twice, once for each study device.

End point type	Secondary

End point timeframe:

Baseline (defined as the last non-missing assessment prior to the 1st dose of study medication), Week 12

End point values	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	271[19]	265[20]		
Units: units on a scale				
least squares mean (standard error)	0.316 (± 0.088)	-0.012 (± 0.089)		

Notes:

[19] - subjects who contributed at least once to the analysis

[20] - subjects who contributed at least once to the analysis

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BF SPIROMAX (per protocol) v SYMBICORT TURBOHALER (per protocol)
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [21]
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	0.328
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.51

Notes:

[21] - Analyzed using an ANCOVA model with effects due to baseline score, gender, age, and treatment, imputing missing data via LOCF.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening visit (Day −14 ± 2 days) through Week 12 or early termination (up to Day 84 ±2 days)

Adverse event reporting additional description:

Adverse events for Treatment Period are presented in this table. Non-serious adverse events for Run-in period are attached to this record (EudraCT system restrictions prevented their addition within the record). There were no serious adverse events during the run-in period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Treatment Period: BF SPIROMAX

Reporting group description:

2 inhalations of BF Spiromax at a dosage of 160/4.5 mcg (budesonide/formoterol fumarate dihydrate 160/4.5 mcg) and 2 inhalations of SYMBICORT placebo administered twice daily (AM and PM) during the 12-week treatment period.

Reporting group title	Treatment Period: SYMBICORT TURBOHALER

Reporting group description: -

Serious adverse events	Treatment Period: BF SPIROMAX	Treatment Period: SYMBICORT TURBOHALER	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 303 (0.33%)	3 / 299 (1.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
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			
Intervertebral disc protrusion			

subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (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: 0 %

Non-serious adverse events	Treatment Period: BF SPIROMAX	Treatment Period: SYMBICORT TURBOHALER	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	116 / 303 (38.28%)	104 / 299 (34.78%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 303 (0.33%)	3 / 299 (1.00%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 303 (1.98%)	2 / 299 (0.67%)	
occurrences (all)	8	2	
Chest discomfort			
subjects affected / exposed	2 / 303 (0.66%)	0 / 299 (0.00%)	
occurrences (all)	2	0	
Influenza like illness			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Feeling cold			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast			

disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Epididymitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Dysmenorrhoea			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 303 (3.63%)	8 / 299 (2.68%)	
occurrences (all)	12	9	
Oropharyngeal pain			
subjects affected / exposed	7 / 303 (2.31%)	5 / 299 (1.67%)	
occurrences (all)	7	8	
Dysphonia			
subjects affected / exposed	9 / 303 (2.97%)	1 / 299 (0.33%)	
occurrences (all)	9	1	
Dyspnoea			
subjects affected / exposed	4 / 303 (1.32%)	4 / 299 (1.34%)	
occurrences (all)	4	9	
Rhinorrhoea			
subjects affected / exposed	2 / 303 (0.66%)	1 / 299 (0.33%)	
occurrences (all)	2	1	
Epistaxis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 299 (0.33%)	
occurrences (all)	1	1	
Throat irritation			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Rhonchi			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Pulmonary congestion			

subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	2	
Sneezing			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Dry throat			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Aspiration			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Pharyngeal inflammation			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Nasal obstruction			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Increased upper airway secretion			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Pleurisy			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	

Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 303 (0.00%)	2 / 299 (0.67%)	
occurrences (all)	0	4	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 303 (0.99%)	0 / 299 (0.00%)	
occurrences (all)	3	0	
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Head injury			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Wrist fracture			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Animal scratch			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 303 (0.99%)	0 / 299 (0.00%)	
occurrences (all)	4	0	
Angina pectoris			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			

subjects affected / exposed	18 / 303 (5.94%)	24 / 299 (8.03%)	
occurrences (all)	31	57	
Dizziness			
subjects affected / exposed	1 / 303 (0.33%)	2 / 299 (0.67%)	
occurrences (all)	1	2	
Migraine			
subjects affected / exposed	1 / 303 (0.33%)	1 / 299 (0.33%)	
occurrences (all)	3	1	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	2	
Hyposmia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Radiculitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Aphonia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Cataract			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 303 (1.32%)	1 / 299 (0.33%)	
occurrences (all)	5	1	
Diarrhoea			

subjects affected / exposed	5 / 303 (1.65%)	2 / 299 (0.67%)	
occurrences (all)	5	3	
Abdominal pain			
subjects affected / exposed	1 / 303 (0.33%)	3 / 299 (1.00%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	2 / 303 (0.66%)	1 / 299 (0.33%)	
occurrences (all)	4	1	
Gastritis			
subjects affected / exposed	2 / 303 (0.66%)	1 / 299 (0.33%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	0 / 303 (0.00%)	2 / 299 (0.67%)	
occurrences (all)	0	3	
Toothache			
subjects affected / exposed	0 / 303 (0.00%)	2 / 299 (0.67%)	
occurrences (all)	0	2	
Dry mouth			
subjects affected / exposed	1 / 303 (0.33%)	1 / 299 (0.33%)	
occurrences (all)	1	1	
Aphthous stomatitis			
subjects affected / exposed	2 / 303 (0.66%)	0 / 299 (0.00%)	
occurrences (all)	5	0	
Constipation			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Tongue discolouration			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Diverticulum			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Tooth loss			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Stomatitis			

subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 303 (0.33%)	2 / 299 (0.67%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	0 / 303 (0.00%)	2 / 299 (0.67%)	
occurrences (all)	0	2	
Dermatitis contact			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	2	
Skin lesion			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 303 (1.32%)	1 / 299 (0.33%)	
occurrences (all)	4	1	
Muscle spasms			
subjects affected / exposed	1 / 303 (0.33%)	3 / 299 (1.00%)	
occurrences (all)	1	4	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 303 (0.33%)	1 / 299 (0.33%)	
occurrences (all)	1	1	
Osteoarthritis			

subjects affected / exposed	2 / 303 (0.66%)	0 / 299 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	2	0	
Pain in jaw			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Osteochondritis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Costochondritis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Arthritis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Rhinitis			
subjects affected / exposed	6 / 303 (1.98%)	7 / 299 (2.34%)	
occurrences (all)	7	7	
Nasopharyngitis			
subjects affected / exposed	31 / 303 (10.23%)	25 / 299 (8.36%)	
occurrences (all)	36	27	
Bronchitis			
subjects affected / exposed	3 / 303 (0.99%)	7 / 299 (2.34%)	
occurrences (all)	3	8	

Influenza			
subjects affected / exposed	2 / 303 (0.66%)	6 / 299 (2.01%)	
occurrences (all)	2	9	
Pharyngitis			
subjects affected / exposed	4 / 303 (1.32%)	4 / 299 (1.34%)	
occurrences (all)	4	4	
Upper respiratory tract infection			
subjects affected / exposed	4 / 303 (1.32%)	3 / 299 (1.00%)	
occurrences (all)	5	3	
Sinusitis			
subjects affected / exposed	1 / 303 (0.33%)	3 / 299 (1.00%)	
occurrences (all)	1	3	
Tonsillitis			
subjects affected / exposed	1 / 303 (0.33%)	3 / 299 (1.00%)	
occurrences (all)	1	3	
Respiratory tract infection viral			
subjects affected / exposed	2 / 303 (0.66%)	2 / 299 (0.67%)	
occurrences (all)	3	3	
Gastroenteritis			
subjects affected / exposed	1 / 303 (0.33%)	2 / 299 (0.67%)	
occurrences (all)	1	2	
Laryngitis			
subjects affected / exposed	1 / 303 (0.33%)	2 / 299 (0.67%)	
occurrences (all)	1	2	
Respiratory tract infection			
subjects affected / exposed	1 / 303 (0.33%)	2 / 299 (0.67%)	
occurrences (all)	1	2	
Viral pharyngitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 303 (0.00%)	2 / 299 (0.67%)	
occurrences (all)	0	2	

Oral candidiasis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 299 (0.33%)	
occurrences (all)	1	1	
Viral rhinitis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 299 (0.33%)	
occurrences (all)	1	1	
Gastrointestinal infection			
subjects affected / exposed	1 / 303 (0.33%)	1 / 299 (0.33%)	
occurrences (all)	1	1	
Candidiasis			
subjects affected / exposed	2 / 303 (0.66%)	0 / 299 (0.00%)	
occurrences (all)	2	0	
Acute tonsillitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	3	
Chronic sinusitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Urethritis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Pharyngotonsillitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Lice infestation			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (all)	0	1	

Respiratory tract infection bacterial			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Tracheitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Infected bites			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Gingival infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26987997