

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

6XPPDU\

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
5HVXOWV LQIRUPDWLRQ	
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)

7ULDO LQIRUPDWLRQ

7ULDO LGHQWLILFDWLRQ	
Sponsor protocol code	BFS-AS-306
\$GGLWLRQDO VWXG\ LGHQWLILHUV	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01803555
WHO universal trial number (UTN)	-

Notes:

6 S R Q V R U V	
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
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Notes:

3DHGLDWULF UHJXODWRU\ GHWDLOV	
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:

5HVXOWV DQDO\VLV VWDJH	
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

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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
- 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:

3RSXODWLRQ RI WULDO VXEMHFWV	
6XEMHFWV HQUROOHG SHU FRXQWU\	
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

EU-CTR publication date: 27 May 2016

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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

6XEMHFWV HQUROOHG SHU DJH JURXS	
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

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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.

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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.

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Number of subjects started	671
Number of subjects completed	605

3UH DVVLJQPHQW VXEMH	IFW QRQ FRPSOHWLRQ UHDVRQV
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

3 H U L R G

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.

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Are arms mutually exclusive?	Yes
\$UP WLWOH	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.

\$UP WLWOH	SYMBICORT TURBOHALER
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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.

1XPEHU RI VXEMHFWV LC) Տեր⊧ԱյիՎROMAX	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

[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.

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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
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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.

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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.

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End point timeframe:

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

(QG SRLQW YDOXHV	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 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.

creatificite 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.

6HFRQGDU\ &KDQJH LQ :HHNO\ \$YHUDJH RI 'DLO\ 7URXJK (YHQLQJ 30 %DVHOLQH 2YHU WKH ZHHN 7UHDWPHQW 3HULRG

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.

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End point timeframe:

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

(QG SRLQW YDOXHV	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)	

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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.

6HFRQGDU\ &KDQJH)URP %DVHOLQH 2YHU WKH ZHI 3HUFHQWDJH RI 6\PSWRP IUHH KRXU 3HULRGV

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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

(QG SRLQW YDOXHV	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)			
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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

6HFRQGDU\ &KDQJH)URP %DVHOLQH 2YHU WKH :HHN 7UHDWPHQW 3H 3HUFHQWDJH RI 5HVFXH)UHH +RXU 3HULRGV

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
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End point timeframe:

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

(QG SRLQW YDOXHV	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)	

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6WDWLVWLFDO DQDO\VL	StaNdtiWallOAmhalysis 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

6HFRQGDU\ &KDQJH)URP %DVHOLQH LQ 7URXJK)RUFHG ([SLUDWRU\ 9F))(9 2YHU WKH :HHN 7UHDWPHQW 3HULRG

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

(QG SRLQW YDOXHV	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

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	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

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

6HFRQGDU\ &KDQJH)URP %DVHOLQH LQ 3DWLHQW 6DWLVIDFWLRQ DQG 4XHVWLRQQDLUH IRU ,QKDODWLRQ 'HYLFHV 3\$6\$34 2YHUDOO 6DWLVID :HHN 7UHDWPHQW 3HULRG

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
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End point timeframe:

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

(QG SRLQW YDOXHV	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

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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

[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.

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·	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
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End point timeframe:

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

(QG SRLQW YDOXHV	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

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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

[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.

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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.

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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
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End point timeframe:

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

(QG SRLQW YDOXHV	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	

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

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

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6WDWLVWLFDO DQDO\VL	StaMid±ikWallOAmhalysis 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

6HFRQGDU\ &KDQJH)URP %DVHOLQH LQ 3\$6\$34 :LOOLQJQHVV WR &RQW'HYLFH 6FRUHV 2YHU WKH :HHN 7UHDWPHQW 3HULRG

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
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End point timeframe:

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

(QG SRLQW YDOXHV	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

6WDWLVWLFDO DQDO\VHV

6WDWLVWLFDO DQDO\VL	StaMid±ikWallOAmhalysis 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.

6HFRQGDU\ &KDQJH)URP %DVHOLQH LQ 2YHUDOO ,QKDOHU 4XLFNQHVV

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

(per protocol) (per protocol)	TOG SELOW YDOXAV I	BF SPIROMAX (per protocol)	SYMBICORT TURBOHALER (per protocol)		
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\$GYHUVH HYHQWV LQIRUPDWLRQ

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.

record). There were no serious duverse e	erits during the run in period.
Assessment type	Systematic
'LFWLRQDU\ XVHG	
Dictionary name	MedDRA
Dictionary version	16.0
5HSRUWLQJ JURXSV	

Reporting group description:

Reporting group title

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.

Treatment Period: BF SPIROMAX

ODE TURBOULD ED
ORT TURBOHALER
(

Reporting group description: -

6HULRXV DGYHUVH HYHC	Treatment Period: W 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 %

1RQ VHULRXV DGYHUVH	H 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 / 202 /2 (20/)	0 / 200 /2 (00/)	
occurrences (all)	11 / 303 (3.63%)	8 / 299 (2.68%)	
occurrences (aii)	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	
	7	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 / 303 (0.00%)	1 / 299 (0.33%)	
occurrences (un)			
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 / 202 /0 000/)	1 / 200 /0 220/)	
	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 / 233 (0.00 /0)	
(4.1.)	1	U	
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)			
occurrences (aii)	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	
, ,	1	Ŭ	
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	
, ,		Ŭ	
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 / 302 /1 220/ \	1 / 200 /0 220/ \
occurrences (all)	4 / 303 (1.32%)	1 / 299 (0.33%) 1
		1
Diarrhoea	1	

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 occurrences (all)	1 / 303 (0.33%) 1	0 / 299 (0.00%) 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 / 303 (1.32 %)	1 / 299 (0.5570)	
	, i	<u> </u>	
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			

occurrences (all) 2 0 Myalgia subjects affected / exposed occurrences (all) 0 / 303 (0.00%) 1 / 299 (0.33%) occurrences (all) 0 1 Tendonitis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Pain in jaw subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Pain in extremity subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Osteochondritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Neck pain subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Costochondritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Arthritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%)	subjects affected / exposed	2 / 303 (0.66%)	0 / 299 (0.00%)
Myalgia subjects affected / exposed occurrences (all) 0 / 303 (0.00%) 1 / 299 (0.33%) Tendonitis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Pain in jaw subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Pain in extremity subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Osteochondritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Neck pain subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Occurrences (all) 1 0 Arthritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Infections and infestations Rhinitis subjects affected / exposed occurrences (all) 6 / 303 (1.98%) 7 / 299 (2.34%) Nasopharyngitis subjects affected / exposed occurrences (all) 31 / 303 (10.23%) 25 / 299 (8.36%) Peronchitis subjects affected / exposed occurrences (all) 36 27			
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Tendonitis Subjects affected / exposed 1 / 303 (0.33%) 0 / 299 (0.00%) 0 /		0 / 202 /0 222/	4 / 202 /2
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subjects affected / exposed occurrences (all) Pain in jaw subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Osteochondritis subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Costochondritis subjects affected / exposed occurrences (all) Costochondritis subjects affected / exposed occurrences (all) Costochondritis subjects affected / exposed occurrences (all) Infections and infestations Rhinitis subjects affected / exposed occurrences (all) Nasopharyngitis occurrences (all)	occurrences (an)	0	1
Description occurrences (all) 2	Tendonitis		
Pain in jaw subjects affected / exposed occurrences (all) 1 0 0 Pain in extremity subjects affected / exposed occurrences (all) 1 0 0 Osteochondritis subjects affected / exposed occurrences (all) 1 0 0 Neck pain subjects affected / exposed occurrences (all) 1 0 0 Neck pain subjects affected / exposed occurrences (all) 1 0 0 Costochondritis subjects affected / exposed occurrences (all) 1 0 0 Costochondritis subjects affected / exposed occurrences (all) 1 0 0 Arthritis subjects affected / exposed occurrences (all) 1 0 0 Infections and infestations Rhinitis subjects affected / exposed occurrences (all) 7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)
subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Osteochondritis subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Costochondritis subjects affected / exposed occurrences (all) I 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	occurrences (all)	2	0
occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Osteochondritis subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Costochondritis subjects affected / exposed occurrences (all) 1 0 Neck pain subjects affected / exposed occurrences (all) 1 0 Costochondritis subjects affected / exposed occurrences (all) 1 0 Arthritis subjects affected / exposed occurrences (all) 1 O Infections and infestations Rhinitis subjects affected / exposed occurrences (all) 7 Nasopharyngitis subjects affected / exposed occurrences (all) 7 Nasopharyngitis subjects affected / exposed occurrences (all) 3 3 3 3 3 3 3 3 3 3 3 3 3	Pain in jaw		
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subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Osteochondritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Neck pain subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Occurrences (all) 1 0 Costochondritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Arthritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Infections and infestations Rhinitis subjects affected / exposed occurrences (all) 6 / 303 (1.98%) 7 / 299 (2.34%) Nasopharyngitis subjects affected / exposed occurrences (all) 31 / 303 (10.23%) 25 / 299 (8.36%) Bronchitis subjects affected / exposed occurrences (all) 3 / 303 (0.99%) 7 / 299 (2.34%)	occurrences (all)	1	0
subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Osteochondritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Neck pain subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Occurrences (all) 1 0 Costochondritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Arthritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Infections and infestations Rhinitis subjects affected / exposed occurrences (all) 6 / 303 (1.98%) 7 / 299 (2.34%) Nasopharyngitis subjects affected / exposed occurrences (all) 31 / 303 (10.23%) 25 / 299 (8.36%) Bronchitis subjects affected / exposed occurrences (all) 3 / 303 (0.99%) 7 / 299 (2.34%)	Pain in extremity		
Occurrences (all) Osteochondritis subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Costochondritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) 0 /	· ·	1 / 303 (0.33%)	0 / 299 (0.00%)
subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Costochondritis subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Infections and infestations Rhinitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) 31 / 303 (0.33%) 0 / 299 (0.00%) 0	occurrences (all)		
subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Costochondritis subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Infections and infestations Rhinitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) 31 / 303 (0.99%) 7 / 299 (0.00%) 0 / 299 (0.			-
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subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Arthritis subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) occurrences (all) 1 0 Infections and infestations Rhinitis subjects affected / exposed occurrences (all) 6 / 303 (1.98%) 7 / 299 (2.34%) Nasopharyngitis subjects affected / exposed occurrences (all) 31 / 303 (10.23%) 25 / 299 (8.36%) Bronchitis subjects affected / exposed 3 / 303 (0.99%) 7 / 299 (2.34%)	occurrences (all)	1	0
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Arthritis subjects affected / exposed occurrences (all) Infections and infestations Rhinitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Particular of the composed of the composed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed 3 / 303 (0.99%) 7 / 299 (0.00%) 0 / 299 (0.00%) 7 / 299 (2.34%) 7 / 299 (2.34%)	subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)
subjects affected / exposed occurrences (all) 1 / 303 (0.33%) 0 / 299 (0.00%) Infections and infestations Rhinitis subjects affected / exposed occurrences (all) 6 / 303 (1.98%) 7 / 299 (2.34%) Nasopharyngitis subjects affected / exposed occurrences (all) 31 / 303 (10.23%) 25 / 299 (8.36%) Bronchitis subjects affected / exposed 3 / 303 (0.99%) 7 / 299 (2.34%)	occurrences (all)	1	0
subjects affected / exposed 1 / 303 (0.33%) 0 / 299 (0.00%) occurrences (all) 1 0 Infections and infestations 7 7 Rhinitis 6 / 303 (1.98%) 7 / 299 (2.34%) occurrences (all) 7 7 Nasopharyngitis 31 / 303 (10.23%) 25 / 299 (8.36%) occurrences (all) 36 27 Bronchitis 3 / 303 (0.99%) 7 / 299 (2.34%)	Arthritis		
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Rhinitis 6 / 303 (1.98%) 7 / 299 (2.34%) occurrences (all) 7 7 Nasopharyngitis 31 / 303 (10.23%) 25 / 299 (8.36%) occurrences (all) 36 27 Bronchitis 3 / 303 (0.99%) 7 / 299 (2.34%)	occurrences (all)		0
Rhinitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) 31 / 303 (1.98%) 7 / 299 (2.34%) 7 Nasopharyngitis subjects affected / exposed occurrences (all) 36 27 Bronchitis subjects affected / exposed 3 / 303 (0.99%) 7 / 299 (2.34%)	Infactions and infactations		
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Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed 3 / 303 (0.99%) 3 / 299 (8.36%) 7 / 299 (2.34%)	subjects affected / exposed	6 / 303 (1.98%)	7 / 299 (2.34%)
subjects affected / exposed 31 / 303 (10.23%) 25 / 299 (8.36%) occurrences (all) 36 27 Bronchitis 3 / 303 (0.99%) 7 / 299 (2.34%)	occurrences (all)	7	7
subjects affected / exposed 31 / 303 (10.23%) 25 / 299 (8.36%) occurrences (all) 36 27 Bronchitis 3 / 303 (0.99%) 7 / 299 (2.34%)	Nasonharyngitis		
occurrences (all) 36 27 Bronchitis subjects affected / exposed 3 / 303 (0.99%) 7 / 299 (2.34%)		31 / 303 (10.23%)	25 / 299 (8.36%)
Bronchitis subjects affected / exposed 3 / 303 (0.99%) 7 / 299 (2.34%)			
subjects affected / exposed 3 / 303 (0.99%) 7 / 299 (2.34%)			
() () () () () () () () () ()		2 / 202 / 2 000/ 2	7 / 200 /2 2 /2/2
3 8			
	occurrences (an)	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 / 299 (1.00 /0)	
		-	
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 infaction			
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 / 005 / 0 /		
	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		
வெற்று செர்கள்கள்கள்கள்கள்கள்கள்கள்கள்கள்கள்கள்கள்	2 / 303 (0.66%)	0 / 299 (0.00%)
occurrences (all)	Q	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		1 / 299 (0.33%)

	I] I	
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)			
222	1	0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 303 (0.33%)	0 / 299 (0.00%)	
occurrences (all)	3	0	

ORUH LQIRUPDWLRQ

6XEVWDQWLDO SURWRFRO DPHQGPHQWV JOREDOO\

Were there any global substantial amendments to the protocol? No

,QWHUUXSWLRQV JOREDOO\

Were there any global interruptions to the trial? No

/LPLWDWLRQV DQG FDYHDWV

None reported

2QOLQH UHIHUHQFHV

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