Clinical trial results:
A Double-Blind, Double-Dummy, Randomised, Placebo- And Active-Controlled, Three-Way Crossover Study to Evaluate the Effect of Budesonide/Formoterol Spiromax® 80/4.5 mcg Inhalation Powder and Symbicort® Turbohaler® 100/6 mcg on the Short-Term Lower Leg Growth Rate in Prepubescent Children With Persistent Asthma

Summary

EudraCT number	2010-019082-29
Trial protocol	DK
Global end of trial date	26 January 2011

Results information

Result version number	v1 (current)
This version publication date	23 March 2019
First version publication date	23 March 2019

Trial information

Trial identification

Sponsor protocol code	BFS-AS-305

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	74 NW, 176th Street, Miami, FL, United States, 33169
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 001 215-591-3000, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 001 215-591-3000, info.eraclinical@teva.de

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	26 January 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate the non-inferiority of Budesonide/Formoterol Spiromax® 80/4.5 micrograms (mcg) Inhalation Powder (Budesonide Formoterol [BF] Spiromax) relative to Symbicort® Turbohaler® 100/6 mcg (Symbicort Turbohaler) on short-term growth rate of the right lower leg as measured by knemometry in prepubescent children with persistent asthma.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the US Code of Federal Regulations (Title 21, CFR Parts 50, 56 and 312), European Union (EU) Directives (where applicable), with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonization (ICH) of Technical Requirements of Pharmaceuticals for Human Use guidelines, and in accordance with local regulations and legal requirements.
The study was conducted with due attention to the rights of children. The interest of the children always prevailed over those of science and society.

Background therapy:

Participants were allowed to take short-acting beta agonist (SABA) therapy throughout the study (during 2-week run-in period, 2-week wash-out periods, and 3 treatment periods [2 weeks each]).

Evidence for comparator: -

Actual start date of recruitment	27 September 2010
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	Denmark: 77
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	77
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 81 participants were screened, of which 4 participants were screen failures. A total of 77 participants were randomized and treated in 1 of the 6 different treatment sequences, after the 14-day run-in period.

Period 1

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

Arms

Arm title	All Participants

Arm description:

All participants were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA), each of which was comprised of the same 3 interventions (A, B, and C). Treatment A consisted of 2 oral inhalations of Budesonide 80 mcg/Formoterol 4.5 mcg (BF SPIROMAX®) (active treatment) in morning (AM) and 2 oral inhalations in evening (PM) along with 2 oral inhalations of Turbohaler placebo both in AM and PM. Treatment B consisted of 2 oral inhalations of Budesonide 100 mcg/Formoterol 6 mcg (Symbicort® Turbohaler®) (comparator) in AM and 2 oral inhalations in PM along with 2 oral inhalations of Spiromax placebo both in AM and PM. Treatment C consisted of 2 oral inhalations of Spiromax placebo in AM and 2 oral inhalations in PM along with 2 oral inhalations of Turbohaler placebo both in AM and PM. The study included 3 treatment periods which were 14 days (+/-4 days) each. Treatment Periods 1 and 2 were followed by a 14-day Washout Period (+/-4 days).

Arm type	Experimental
Investigational medicinal product name	BF SPIROMAX®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg; administered as oral inhalations.

Investigational medicinal product name	Symbicort® Turbohaler®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Budesonide 100 mcg and formoterol fumarate dihydrate 6 mcg; administered as oral inhalations.

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

Dosage and administration details:

Spiromax placebo administered as oral inhalations.

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

Dosage and administration details:

Turbohaler placebo administered as oral inhalations.

Number of subjects in period 1	All Participants
Started	77
Received at least 1 dose of study drug	77
Intent-to-treat (ITT) population	76
Completed	73
Not completed	4
Consent withdrawn by subject	3
Adverse event	1

Baseline characteristics

Reporting groups	
Reporting group title	All Participants

Reporting group description:

All participants were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA), each of which was comprised of the same 3 interventions (A, B, and C). Treatment A consisted of 2 oral inhalations of Budesonide 80 mcg/Formoterol 4.5 mcg (BF SPIROMAX®) (active treatment) in morning (AM) and 2 oral inhalations in evening (PM) along with 2 oral inhalations of Turbohaler placebo both in AM and PM. Treatment B consisted of 2 oral inhalations of Budesonide 100 mcg/Formoterol 6 mcg (Symbicort® Turbohaler®) (comparator) in AM and 2 oral inhalations in PM along with 2 oral inhalations of Spiromax placebo both in AM and PM. Treatment C consisted of 2 oral inhalations of Spiromax placebo in AM and 2 oral inhalations in PM along with 2 oral inhalations of Turbohaler placebo both in AM and PM. The study included 3 treatment periods which were 14 days (+/-4 days) each. Treatment Periods 1 and 2 were followed by a 14-day Washout Period (+/-4 days).

Reporting group values	All Participants	Total	
Number of subjects	77	77	
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	8.6		
standard deviation	± 1.51	-	
Gender Categorical			
Units: Subjects			
Female	31	31	
Male	46	46	

End points

End points reporting groups

Reporting group title	All Participants

Reporting group description:

All participants were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA), each of which was comprised of the same 3 interventions (A, B, and C). Treatment A consisted of 2 oral inhalations of Budesonide 80 mcg/Formoterol 4.5 mcg (BF SPIROMAX®) (active treatment) in morning (AM) and 2 oral inhalations in evening (PM) along with 2 oral inhalations of Turbohaler placebo both in AM and PM. Treatment B consisted of 2 oral inhalations of Budesonide 100 mcg/Formoterol 6 mcg (Symbicort® Turbohaler®) (comparator) in AM and 2 oral inhalations in PM along with 2 oral inhalations of Spiromax placebo both in AM and PM. Treatment C consisted of 2 oral inhalations of Spiromax placebo in AM and 2 oral inhalations in PM along with 2 oral inhalations of Turbohaler placebo both in AM and PM. The study included 3 treatment periods which were 14 days (+/-4 days) each. Treatment Periods 1 and 2 were followed by a 14-day Washout Period (+/-4 days).

Subject analysis set title	BF Spiromax
Subject analysis set type	Per protocol

Subject analysis set description:

Budesonide 80 mcg/Formoterol 4.5 mcg, two oral inhalations in morning and two oral inhalations in evening in each treatment period.

Subject analysis set title	Symbicort Turbohaler
Subject analysis set type	Per protocol

Subject analysis set description:

Budesonide 100 mcg/Formoterol 6 mcg, two oral inhalations in morning and two oral inhalations in evening in each treatment period.

Subject analysis set title	Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Spiromax placebo or Turbohaler placebo, two oral inhalations in morning and two oral inhalations in evening in each treatment period.

Primary: Short-Term Lower Leg Growth Rate (LLGR) of The Right Lower Leg

End point title	Short-Term Lower Leg Growth Rate (LLGR) of The Right Lower Leg

End point description:

Short-term LLGR was measured by knemometry of the right lower leg after 2 weeks of treatment, and was calculated for each participant and for each treatment period in millimeters per week (mm/week). Four measurements were taken at each visit, with summaries and analysis based on the mean of the last three results. The LLGR was then determined from the change in growth measurement and number of days in each period; that is, LLGR (mm/week) = ([length in mm (end) - length in mm (start)]/[date (end) - date (start)] + 1) * 7. Per-protocol (PP) population included all data from the ITT population (included all randomised participants who received at least one dose of randomised study medication and had at least one post-baseline assessment.) obtained prior to experiencing major protocol violations.

End point type	Primary

End point timeframe:

Treatments periods 1, 2, and 3 (each treatment period = 2 weeks)

End point values	BF Spiromax	Symbicort Turbohaler	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	70	70	
Units: mm/week				
arithmetic mean (standard deviation)	0.052 (± 0.3396)	0.134 (± 0.3605)	0.247 (± 0.3901)	

Statistical analyses

Statistical analysis title	BF Spiromax vs. Symicort Turbohaler

Statistical analysis description:

Actual number of participants analysed=70. Analysis was performed using ANOVA model with fixed effects of treatment, sequence, and period, a random effect of participant within sequence. Non-inferiority was demonstrated if the lower limit of the 95% two-sided confidence interval for the treatment difference in the short-term LLGR (BF Spiromax minus Symbicort Turbohaler) was greater than -0.200 mm/week.

Comparison groups	BF Spiromax v Symbicort Turbohaler
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Least square (LS) mean difference
Point estimate	-0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.203
upper limit	0.032

Secondary: Change From Period-Specific Baseline in Daily Trough Morning (AM) and Evening (PM) Peak Expiratory Flow (PEF) Rate at End of Each Treatment Period

End point title	Change From Period-Specific Baseline in Daily Trough Morning (AM) and Evening (PM) Peak Expiratory Flow (PEF) Rate at End of Each Treatment Period

End point description:

PEF was determined twice daily, in AM and in PM, before administration of study medications or rescue bronchodilator during run-in period and throughout study. AM PEF was calculated as daily average of AM PEF over the previous 7 days prior to beginning of each treatment period with at least 4 days of non-missing values. The period-specific baseline trough AM PEF was calculated as daily average of AM PEF over each 2-week treatment period with at least 4 days of non-missing values. If non-missing days in each period was less than 4 days, the values were treated as missing. PM PEF and period-specific baseline trough PM PEF was calculated in a manner similar to AM PEF. PP population included all data from ITT population (included all randomised participants who received at least 1 dose of randomised study medication and had at least 1 post-baseline assessment.) obtained prior to experiencing major protocol violations. Here, "n" = number of participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, at end of treatment period 1, 2 and 3 (each treatment period = 2 weeks)

End point values	BF Spiromax	Symbicort Turbohaler	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	70	70	
Units: L/min				
arithmetic mean (standard deviation)				
AM PEF: Change at Period 1 (n=22,23,25)	18.74 (± 24.064)	17.13 (± 17.325)	-1.98 (± 15.764)	
AM PEF: Change at Period 2 (n=25,24,19)	15.45 (± 17.967)	13.50 (± 20.372)	0.38 (± 13.293)	
AM PEF: Change at Period 3 (n=21,22,25)	23.34 (± 21.007)	17.60 (± 13.274)	2.14 (± 11.547)	
PM PEF: Change at Period 1 (n=23,24,25)	16.88 (± 24.914)	16.80 (± 16.895)	-2.30 (± 15.351)	
PM PEF: Change at Period 2 (n=25,24,19)	14.48 (± 17.354)	15.62 (± 23.915)	2.48 (± 18.410)	
PM PEF: Change at Period 3 (n=21,22,25)	17.88 (± 19.827)	15.19 (± 14.886)	2.78 (± 12.445)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Period-Specific Baseline in Percentage of Rescue-Free Days at End of Each Treatment Period

End point title	Change From Period-Specific Baseline in Percentage of Rescue-Free Days at End of Each Treatment Period

End point description:

Participants recorded their use of rescue medication twice daily (AM and PM) before intake of study medications. For the purpose of this study, a "day" was the combination of AM and PM in a 24-hour period. Percentage of days rescue medication taken was calculated as: (Number of days with puffs = 0 / Number of non-missing days (>=4 days)*100. Period-specific baseline was defined as percentage of rescue-free days over the last 7 days prior to the beginning of each treatment period with at least 4 days of non-missing values. A non-missing day was defined as a day in which rescue medication records were non-missing in either the AM or PM or both. PP population included all data from the ITT population (included all randomised participants who received at least one dose of randomised study medication and had at least one post-baseline assessment.) obtained prior to experiencing major protocol violations. Here, "n" signifies number of participants evaluable at specified treatment period.

End point type	Secondary

End point timeframe:

Baseline, at end of treatment period 1, 2 and 3 (each treatment period = 2 weeks)

End point values	BF Spiromax	Symbicort Turbohaler	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	70	70	
Units: percentage of days				
arithmetic mean (standard deviation)				
Change at Period 1 (n = 23, 24, 25)	1.08 (± 18.109)	7.00 (± 24.374)	10.91 (± 31.050)	
Change at Period 2 (n= 25, 24, 19)	3.30 (± 17.391)	15.60 (± 38.770)	2.57 (± 18.534)	

Change at Period 3 (n= 21, 22, 26)	9.37 (± 18.378)	11.90 (± 29.572)	9.35 (± 25.633)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Period-Specific Baseline in Inspiratory Flow Rate at End of Each Treatment Period

End point title	Change From Period-Specific Baseline in Inspiratory Flow Rate at End of Each Treatment Period

End point description:

Period-specific baseline was defined as the average of the 3 inspiratory flow rate obtained at the beginning of each treatment period. PP population included all data from the ITT population (included all randomised participants who received at least one dose of randomised study medication and had at least one post-baseline assessment.) obtained prior to experiencing major protocol violations. Since this was a crossover study, a participant could be excluded from one treatment period, but still be included in the PP population for the other treatment periods. Here, "n" signifies number of participants evaluable at specified treatment period.

End point type	Secondary

End point timeframe:

Baseline, at end of treatment period 1, 2 and 3 (each treatment period =2 weeks)

End point values	BF Spiromax	Symbicort Turbohaler	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	70	70	
Units: liters/minute (L/min)				
arithmetic mean (standard deviation)				
Change at the end of Period 1 (n=23, 24, 25)	-4.49 (± 31.247)	8.61 (± 25.517)	-9.31 (± 28.642)	
Change at the end of Period 2 (n=25, 24, 19)	4.87 (± 14.521)	9.37 (± 30.577)	8.33 (± 21.766)	
Change at the end of Period 3 (n=22, 22, 26)	-11.52 (± 25.515)	-12.65 (± 21.092)	-13.33 (± 22.151)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 24-Hour Urinary Cortisol (UC) Excretion

End point title	24-Hour Urinary Cortisol (UC) Excretion

End point description:

UC population included all randomised participants who received at least one dose of randomised study medication, and whose urine samples did not have confounding factors that would affect the interpretation of the results. Here, "n" signifies number of participants evaluable at specified treatment period.

End point type	Other pre-specified

End point timeframe:

Treatment periods 1, 2, and 3 (each treatment period = 2 weeks)

End point values	BF Spiromax	Symbicort Turbohaler	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18	16	17	
Units: nanomols/liter (nmol/L)				
arithmetic mean (standard deviation)				
Period 1 (n=8, 4, 6)	32.14 (± 13.480)	25.75 (± 16.144)	47.63 (± 31.845)	
Period 2 (n=4, 7, 4)	25.05 (± 10.440)	31.99 (± 15.159)	25.40 (± 14.424)	
Period 3 (n=6, 5, 7)	22.48 (± 20.213)	26.56 (± 10.637)	50.84 (± 26.204)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 24-Hour Urinary Cortisol/Creatinine Ratio

End point title	24-Hour Urinary Cortisol/Creatinine Ratio

End point description:

UC population included all randomised participants who received at least one dose of randomised study medication, and whose urine samples did not have confounding factors that would affect the interpretation of the results. Here, "n" signifies number of participants evaluable at specified treatment period.

End point type	Other pre-specified

End point timeframe:

Treatment periods 1, 2, and 3 (each treatment period = 2 weeks)

End point values	BF Spiromax	Symbicort Turbohaler	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18	16	17	
Units: ratio				
arithmetic mean (standard deviation)				
Period 1 (n=8, 4, 6)	9.18 (± 3.917)	10.33 (± 6.370)	8.81 (± 3.923)	
Period 2 (n=4, 7, 4)	14.25 (± 6.185)	13.74 (± 8.691)	5.63 (± 2.326)	
Period 3 (6, 5, 5)	9.12 (± 7.411)	7.50 (± 5.319)	19.38 (± 13.445)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From randomization until end of third treatment period (in total up to approximately 10 weeks)	
Adverse event reporting additional description:	
Safety population included all randomised participants who received at least one dose of randomised study medication.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups	
Reporting group title	BF Spiromax
Reporting group description:	
Budesonide 80 mcg/Formoterol 4.5 mcg, two oral inhalations in morning and two oral inhalations in evening in each treatment period.	
Reporting group title	Placebo
Reporting group description:	
Spiromax placebo or Turbohaler placebo, two oral inhalations in morning and two oral inhalations in evening in each treatment period.	
Reporting group title	Symbicort Turbohaler
Reporting group description:	
Budesonide 100 mcg/Formoterol 6 mcg, two oral inhalations in morning and two oral inhalations in evening in each treatment period.	

Serious adverse events	BF Spiromax	Placebo	Symbicort Turbohaler
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	0 / 75 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	BF Spiromax	Placebo	Symbicort Turbohaler
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 74 (1.35%)	6 / 75 (8.00%)	2 / 75 (2.67%)
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 74 (1.35%)	6 / 75 (8.00%)	2 / 75 (2.67%)
occurrences (all)	1	7	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2010	The purpose of amendment was to remove blood pressure (BP) as a study assessment. BP was included as a study assessment as it was a non-invasive measure and was not anticipated to be problematic to obtain. However, in attempting to obtain BP measurements, the Principal Investigator noted that the study participants were not used to having their BP measured. This caused high levels of anxiety about the BP measurements by many of the study participants with the result that BP measurements may have been artificially elevated in many participants. Anxiety about the BP measurements by many of the study participants was particularly evident during the baseline BP measurements. However, by the time Protocol Amendment 1 had been submitted to the Danish Medicines Agency, the Principal Investigator confirmed that study participants had become accustomed to the BP assessment process and that study participants were no longer anxious about their BP measurements. The Principal Investigator also confirmed that all study participants and their parents were agreeable to have BP assessments for the remainder of the study. Therefore, the request to the Danish Medicines Agency to authorise Protocol Amendment 1 was withdrawn and was not implemented. The study continued using the Final Version, Revision 1 of the Protocol which was dated 21 Sep 2010.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported