Clinical trial results:
A Randomized, Open-Label, Two Period Crossover, Chronic Dosing, 1-Week, Pilot Study to Assess the Efficacy and Safety of Budesonide and Formoterol Fumarate Inhalation Aerosol Administered with a Spacer Compared with Symbicort® Turbuhaler® in Subjects with Severe to Very Severe Chronic Obstructive Pulmonary Disease and Low Peak Inspiratory Flow

Summary

EudraCT number	2019-001801-26
Trial protocol	DE
Global end of trial date	30 December 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	D5980C00023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04078126
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Pepparedsleden 1, Molndal, Sweden,
Public contact	AstraZeneca AB, AstraZeneca AB, +1 8772409479, information.center@astrazeneca.com
Scientific contact	AstraZeneca AB, AstraZeneca AB, +1 8772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 December 2020
Global end of trial reached?	Yes
Global end of trial date	30 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of Budesonide/ Formoterol Fumarate (BFF) MDI administered with a spacer relative to Symbicort Turbuhaler on lung function.

Protection of trial subjects:

Ventolin HFA was provided throughout the study for subjects to take as needed for relief of symptoms.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study randomized 35 subjects at 4 study centers from Jan 2020 to Dec 2020.

Pre-assignment

Screening details:

Subjects were randomized to an open-label, 2 period crossover study comparing BFF MDI administered with a spacer BID with Symbicort Turbuhaler BID. The subjects underwent an intervening two-week washout period where they used Berodual and budesonide MDI BID.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

All subjects randomized

Arms

Arm title	Overall Study

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Symbicort Turbohaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Symbicord Turbohaler 320/9 µg

Investigational medicinal product name	Budesonide and Formoterol Fumarate Metered Dose Inhalation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

BFF MDI 320/9.6 µg

Number of subjects in period 1	Overall Study
Started	35
Completed	31
Not completed	4
Study put on hold due to COVID-19	4

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	35	35	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	11	
From 65-84 years	24	24	
85 years and over	0	0	
Age Continuous			
ITT Population; mean age in years			
Units: Years			
arithmetic mean	65.8		
standard deviation	± 5.5	-	
Sex: Female, Male			
ITT Population; Gender Distribution			
Units: Participants			
Female	19	19	
Male	16	16	
Race (NIH/OMB)			
ITT Population; Race distribution			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	35	35	
More than one race	0	0	
Unknown or Not Reported	0	0	

Subject analysis sets

Subject analysis set title	BFF MDI - mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the ITT Population with post-baseline spirometry data from both treatment periods at Visits 4 and 6.

Subject analysis set title	Symbicort Turbuhaler - mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the ITT Population with post-baseline spirometry data from both treatment periods at Visits 4 and 6.

Subject analysis set title	BFF MDI - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who were randomised to treatment and received at least one dose of study treatment

Subject analysis set title	Symbicort Turbuhaler - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who were randomised to treatment and received at least one dose of study treatment

Reporting group values	BFF MDI - mITT	Symbicort Turbuhaler - mITT	BFF MDI - ITT
Number of subjects	30	30	33
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	6	9
From 65-84 years	24	24	24
85 years and over	0	0	0
Age Continuous			
ITT Population; mean age in years			
Units: Years			
arithmetic mean	66.5	65.8	66.9
standard deviation	± 4.7	± 5.5	± 4.8
Sex: Female, Male			
ITT Population; Gender Distribution			
Units: Participants			
Female	15	15	17
Male	15	15	16
Race (NIH/OMB)			
ITT Population; Race distribution			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	30	30	33
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Symbicort Turbuhaler - ITT		
Number of subjects	35		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	11		
From 65-84 years	24		
85 years and over	0		
Age Continuous			
ITT Population; mean age in years			
Units: Years			
arithmetic mean	66.9		
standard deviation	± 4.8		
Sex: Female, Male			
ITT Population; Gender Distribution			
Units: Participants			
Female	19		
Male	16		
Race (NIH/OMB)			
ITT Population; Race distribution			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	35		
More than one race	0		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Overall Study
Reporting group description: -	
Subject analysis set title	BFF MDI - mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects in the ITT Population with post-baseline spirometry data from both treatment periods at Visits 4 and 6.	
Subject analysis set title	Symbicort Turbuhaler - mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects in the ITT Population with post-baseline spirometry data from both treatment periods at Visits 4 and 6.	
Subject analysis set title	BFF MDI - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who were randomised to treatment and received at least one dose of study treatment	
Subject analysis set title	Symbicort Turbuhaler - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who were randomised to treatment and received at least one dose of study treatment	

Primary: Peak change from baseline in FEV1 within 4 hours post-dose following 1 week of treatment

End point title	Peak change from baseline in FEV1 within 4 hours post-dose following 1 week of treatment[1]
End point description:	
Peak change from baseline in FEV1 within 4 hours post-dose was defined as the maximum of the FEV1 assessments within 4 hours post-dosing at each visit minus baseline, provided that there were at least 2 non-missing values during the first 4 hours post dose.	
End point type	Primary
End point timeframe:	
4 hours post dose after 1 week of treatment	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a pilot study with no formal statistical hypothesis tests. It was to further inform the design and sample size of potential future studies. Improvements due to each treatment relative to baseline were interpreted using the confidence intervals reported.

End point values	BFF MDI - mITT	Symbicort Turbuhaler - mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[2]	30[3]		
Units: Litre				
least squares mean (confidence interval 95%)	0.256 (0.190 to 0.322)	0.274 (0.208 to 0.340)		

Notes:

[2] - mITT used for analysis

[3] - mITT used for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve for change from baseline in FEV1 from 0 to 4 hours (AUC0-4 h) following 1 week of treatment

End point title	Area under the curve for change from baseline in FEV1 from 0 to 4 hours (AUC0-4 h) following 1 week of treatment

End point description:

FEV1 AUC0-4 was calculated using the trapezoidal rule and was normalized by dividing by the time in hours from dosing to the last measurement included (typically 4 hours).

End point type	Secondary

End point timeframe:

0 to 4 hours post dose after 1 week of treatment

End point values	BFF MDI - mITT	Symbicort Turbuhaler - mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[4]	30[5]		
Units: Litre				
least squares mean (confidence interval 95%)	0.194 (0.133 to 0.254)	0.210 (0.149 to 0.271)		

Notes:

[4] - mITT used for analysis

[5] - mITT used for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-dose FEV1 following 1 week of treatment

End point title	Change from baseline in pre-dose FEV1 following 1 week of treatment

End point description:

Change from baseline in pre-dose FEV1 following 1 week of treatment was defined as the 45-minute pre-dose value following 1 week of treatment minus baseline.

End point type	Secondary

End point timeframe:

1 week of treatment

End point values	BFF MDI - mITT	Symbicort Turbuhaler - mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[6]	30[7]		
Units: Litre				
least squares mean (confidence interval 95%)	0.081 (0.030 to 0.131)	0.087 (0.037 to 0.137)		

Notes:

[6] - mITT used for analysis

[7] - mITT used for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 2-hour post-dose inspiratory capacity (IC) following 1 week of treatment

End point title	Change from baseline in 2-hour post-dose inspiratory capacity (IC) following 1 week of treatment

End point description:

Change from baseline in 2-hour post-dose IC following 1 week of treatment was defined as the 2-hour post-dose assessment of IC following 1 week of treatment minus baseline IC.

End point type	Secondary

End point timeframe:

2 hours post dose after 1 week of treatment

End point values	BFF MDI - mITT	Symbicort Turbuhaler - mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[8]	30[9]		
Units: Litre				
least squares mean (confidence interval 95%)	0.379 (0.242 to 0.517)	0.411 (0.275 to 0.548)		

Notes:

[8] - mITT used for analysis

[9] - mITT used for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-dose PIF (InCheck device set to no resistance) following 1 week of treatment

End point title	Change from baseline in pre-dose PIF (InCheck device set to no resistance) following 1 week of treatment

End point description:

Change from baseline in pre-dose PIF (InCheck device set to no resistance) following 1 week of treatment was defined as the pre-dose PIF (InCheck device set to no resistance) following 1 week of treatment minus baseline PIF.

End point type	Secondary

End point timeframe:

1 week of treatment

End point values	BFF MDI - mITT	Symbicort Turbuhaler - mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[10]	30[11]		
Units: Litre/min				
least squares mean (confidence interval 95%)	1.50 (-2.26 to 5.27)	5.11 (1.34 to 8.88)		

Notes:

[10] - mITT used for analysis

[11] - mITT used for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-dose PIF (resistance set equal to Turbohaler S) following 1 week of treatment

End point title	Change from baseline in pre-dose PIF (resistance set equal to Turbohaler S) following 1 week of treatment

End point description:

Change from baseline in pre-dose PIF (resistance set equal to Turbohaler S) following 1 week of treatment was defined as the pre-dose PIF (resistance set equal to Turbohaler S) following 1 week of treatment minus baseline PIF.

End point type	Secondary

End point timeframe:

1 week of treatment

End point values	BFF MDI - mITT	Symbicort Turbuhaler - mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[12]	30[13]		
Units: Litre/min				
least squares mean (confidence interval 95%)	1.13 (-0.78 to 3.03)	3.82 (1.91 to 5.72)		

Notes:

[12] - mITT used for analysis

[13] - mITT used for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-dose PIF (resistance set equal to ELLIPTA) following 1 week of treatment

End point title	Change from baseline in pre-dose PIF (resistance set equal to

	ELLIPTA) following 1 week of treatment

End point description:

Change from baseline in pre-dose PIF (resistance set equal to ELLIPTA) following 1 week of treatment was defined as the pre-dose PIF (resistance set equal to ELLIPTA) following 1 week of treatment minus baseline PIF.

End point type	Secondary

End point timeframe:

1 week of treatment

End point values	BFF MDI - mITT	Symbicort Turbuhaler - mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[14]	30[15]		
Units: Litre/min				
least squares mean (confidence interval 95%)	1.21 (-1.15 to 3.56)	2.74 (0.39 to 5.09)		

Notes:

[14] - mITT used for analysis

[15] - mITT used for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 2-hour post-dose FEV1 following the first dose

End point title	Change from baseline in 2-hour post-dose FEV1 following the first dose

End point description:

Change from baseline in 2-hour post-dose FEV1 following the 1st dose of treatment was defined as the 2-hour post-dose assessment of FEV1 following the 1st dose of treatment (Visit 3 or 5) minus baseline FEV1.

End point type	Secondary

End point timeframe:

1 day (2 hours)

End point values	BFF MDI - mITT	Symbicort Turbuhaler - mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[16]	30[17]		
Units: Litre				
least squares mean (confidence interval 95%)	0.136 (0.100 to 0.173)	0.093 (0.057 to 0.130)		

Notes:

[16] - mITT used for analysis

[17] - mITT used for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 2-hour post-dose IC following the first dose

End point title	Change from baseline in 2-hour post-dose IC following the first dose

End point description:

Change from baseline in 2-hour post-dose IC following the 1st dose of treatment was defined as the 2-hour post-dose assessment of IC following the 1st dose of treatment (Visit 3 or 5) minus baseline IC.

End point type	Secondary

End point timeframe:

1 day (2 hours)

End point values	BFF MDI - mITT	Symbicort Turbuhaler - mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[18]	30[19]		
Units: Litre				
least squares mean (confidence interval 95%)	0.264 (0.164 to 0.363)	0.258 (0.161 to 0.356)		

Notes:

[18] - mITT used for analysis

[19] - mITT used for analysis

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious adverse events were collected from Randomization throughout the Treatment Period and including the washout and follow-up periods.

Adverse event reporting additional description:

The Safety Population was defined as all subjects who were randomized to treatment and received at least one dose of study treatment. Subjects were analyzed according to the treatment actually received. Serious adverse events were recorded from the time of signing of the informed consent form.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Symbicort Turbuhaler

Reporting group description:

Subject treated with Symbicort Turbuhaler

Reporting group title	BFF MDI

Reporting group description:

Subject treated with BFF MDI

Serious adverse events	Symbicort Turbuhaler	BFF MDI	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 35 (0.00%)	0 / 33 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Symbicort Turbuhaler	BFF MDI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 35 (2.86%)	1 / 33 (3.03%)	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 35 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			

subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 33 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2020	Most revisions in the amendment address the impact of study hold and re-start during the COVID-19 pandemic and related local advisories.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	COVID-19 pandemic-related events	17 September 2020

Notes:

Limitations and caveats

None reported