Clinical trial results:
A Randomized, Double-blind, Two Treatment, Two Period, Chronic Dosing (4 weeks), Cross-Over, Multi-Center Pilot Study to Evaluate the Effects of Budesonide/Glycopyrronium/Formoterol Fumarate and Glycopyrronium/Formoterol Fumarate on Specific Image-based Airway Volumes and Resistance in Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease

Summary

EudraCT number	2018-001704-10
Trial protocol	NL BE
Global end of trial date	11 November 2019

Results information

Result version number	v2 (current)
This version publication date	10 February 2021
First version publication date	27 November 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D5980C00019

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Pepparedsleden 1, Molndal, Sweden,
Public contact	Magnus Aurivillius, AstraZeneca AB, magnus.aurivillius@astrazeneca.com
Scientific contact	Magnus Aurivillius, AstraZeneca AB, magnus.aurivillius@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	16 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2019
Global end of trial reached?	Yes
Global end of trial date	11 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of BGF MDI and GFF MDI on specific image-based airway volumes and resistance in subjects with moderate to severe COPD following chronic twice daily (BID) dosing after approximately 4 weeks of treatment.

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	26 February 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	Belgium: 7
Country: Number of subjects enrolled	Netherlands: 16
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	9
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study randomized 23 subjects at 4 study centers (1 center in Belgium and 3 centers in the Netherlands) from 26 February 2019 to 11 November 2019.

Pre-assignment

Screening details:

Subjects were randomized into 1 of 2 treatment sequences. Sequence 1 received BGF MDI in Period 1 followed by GFF MDI in Period 2. Sequence 2 received GFF MDI in Period 1 followed by BGF MDI in Period 2.

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, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

All Subjects Randomized

Arms

Arm title	Overall Study
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Budesonide/Glycopyrronium/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:

BGF MDI 320/14.4/9.6 µg

Investigational medicinal product name	Glycopyrronium/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:

GFF MDI 14.4/9.6 µg

Number of subjects in period 1	Overall Study
Started	23
Completed	21
Not completed	2
Adverse event, non-fatal	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
All Subjects Randomized	

Reporting group values	Overall Study	Total	
Number of subjects	23	23	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age <37 wks)	0	0	
Newborns (0-27 days)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (≥40-<65 years)	9	9	
Adults (≥65-<80 years)	14	14	
Age Continuous Units: years			
arithmetic mean	64.9		
standard deviation	± 7.6	-	
Gender Categorical Units: Subjects			
Female	5	5	
Male	18	18	
Race 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	23	23	
More than one race	0	0	
Unknown or Not Reported	0	0	

Subject analysis sets	
Subject analysis set title	BGF MDI
Subject analysis set type	Intention-to-treat
Subject analysis set description: All Subjects Randomized	
Subject analysis set title	GFF MDI
Subject analysis set type	Intention-to-treat
Subject analysis set description: All Subjects Randomized	

Reporting group values	BGF MDI	GFF MDI	
Number of subjects	22	23	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age <37 wks)	0	0	
Newborns (0-27 days)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (≥40-<65 years)	9	9	
Adults (≥65-<80 years)	13	14	
Age Continuous Units: years			
arithmetic mean	64.8	64.9	
standard deviation	± 7.8	± 7.6	
Gender Categorical Units: Subjects			
Female	5	5	
Male	17	18	
Race 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	22	23	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Overall Study
Reporting group description: -	
Subject analysis set title	BGF MDI
Subject analysis set type	Intention-to-treat
Subject analysis set description: All Subjects Randomized	
Subject analysis set title	GFF MDI
Subject analysis set type	Intention-to-treat
Subject analysis set description: All Subjects Randomized	

Primary: Specific Image-based Airway Volume (siVaw)

End point title	Specific Image-based Airway Volume (siVaw)[1]
End point description: Specific Image-based Airway Volume (siVaw) measured in mL/L. Average across lobes, adjusted for lobe volume. Reported as ratio to baseline.	
End point type	Primary
End point timeframe: Baseline, Day 29	

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: According to the protocol, the primary analysis in this study was not a comparison between treatments, it was a comparison to baseline within each treatment. Therefore, no statistical analysis is included in this form as to only name a single treatment arm for each analysis generated validation errors. The estimates and confidence intervals for each comparison to baseline are however provided.

End point values	BGF MDI	GFF MDI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	21		
Units: Ratio to baseline				
geometric mean (confidence interval 95%)	1.72 (1.38 to 2.13)	1.53 (1.28 to 1.83)		

Statistical analyses

No statistical analyses for this end point

Primary: Specific Image-based Airway Resistance (siRaw)

End point title	Specific Image-based Airway Resistance (siRaw)[2]
End point description: Specific Image-based Airway Resistance (siRaw) measured in kPa·s. Average across lobes, adjusted for lobe volume. Reported as ratio to baseline.	
End point type	Primary
End point timeframe: Baseline, Day 29	

Notes:

[2] - 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: According to the protocol, the primary analysis in this study was not a comparison between treatments, it was a comparison to baseline within each treatment. Therefore, no statistical analysis is included in this form as to only name a single treatment arm for each analysis generated validation errors. The estimates and confidence intervals for each comparison to baseline are however provided.

End point values	BGF MDI	GFF MDI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	21		
Units: Ratio to baseline				
geometric mean (confidence interval 95%)	0.50 (0.39 to 0.63)	0.52 (0.40 to 0.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Image-based Airway Volume (iVaw)

End point title	Image-based Airway Volume (iVaw)

End point description:

Image-based Airway Volume (iVaw) measured in mL. Average across lobes, without adjustment for lobe volume. Reported as ratio to baseline.

End point type	Secondary

End point timeframe:

Baseline, Day 29

End point values	BGF MDI	GFF MDI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	21		
Units: Ratio to baseline				
geometric mean (confidence interval 95%)	1.70 (1.37 to 2.11)	1.51 (1.26 to 1.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Image-based Airway Resistance (iRaw)

End point title	Image-based Airway Resistance (iRaw)

End point description:

Image-based Airway Resistance (iRaw) measured in kPa·s/L. Average across lobes, without adjustment for lobe volume. Reported as ratio to baseline.

End point type	Secondary

End point timeframe:
Baseline, Day 29

End point values	BGF MDI	GFF MDI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	21		
Units: Ratio to baseline				
geometric mean (confidence interval 95%)	0.50 (0.40 to 0.63)	0.52 (0.40 to 0.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Forced Expiratory Volume in 1 Second (Post-dose FEV1)

End point title	Forced Expiratory Volume in 1 Second (Post-dose FEV1)

End point description:
Change from baseline in Forced Expiratory Volume in One Second (Post-dose FEV1)

End point type	Secondary

End point timeframe:
Baseline, Day 29

End point values	BGF MDI	GFF MDI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: Liters				
arithmetic mean (confidence interval 95%)	0.346 (0.182 to 0.509)	0.273 (0.140 to 0.405)		

Statistical analyses

No statistical analyses for this end point

Secondary: Image-based Functional Residual Capacity (FRC)

End point title	Image-based Functional Residual Capacity (FRC)

End point description:
Change from baseline in Functional Residual Capacity (FRC).

End point type	Secondary

End point timeframe:
Baseline, Day 29

End point values	BGF MDI	GFF MDI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	21		
Units: Liters				
arithmetic mean (confidence interval 95%)	-0.28 (-0.77 to 0.21)	-0.50 (-0.81 to -0.18)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Visit 2 throughout the treatment period and including the follow-up period telephone call.

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 and for whom any post-dose data were available. Serious adverse events were collected from Visit 2 throughout the treatment period and including the follow-up period telephone call.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	BGF MDI

Reporting group description:

Budesonide/Glycopyrronium/Formoterol Fumarate Metered Dose Inhalation

Reporting group title	GFF MDI

Reporting group description:

Glycopyrronium/Formoterol Fumarate Metered Dose Inhalation

Serious adverse events	BGF MDI	GFF MDI	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BGF MDI	GFF MDI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 23 (8.70%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported