Clinical trial results:
The efficacy and safety of new formulation of combination of fluticasone propionate / salmeterol (125g / 25g) in MDI HFA inhaler compared with the reference drug at a dose of 500g / 50g in DPI (dry powder inhaler) type disc in patients with chronic asthma

Summary

EudraCT number	2017-000735-14
Trial protocol	PL
Global end of trial date	27 February 2020

Results information

Result version number	v1 (current)
This version publication date	04 March 2021
First version publication date	04 March 2021
Summary attachment (see zip file)	Study Summary (20200914_1_Summary.docx)

Trial information

Trial identification

Sponsor protocol code	L-A/2017/COM/01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	LEK-AM Sp. z o.o.
Sponsor organisation address	ul. Ostrzykowizna 14A, Zakroczym, Poland, 05-170
Public contact	Deputy General Manager, QAH Sp. z o.o. Sp. k., +48 426563048, mateusz.jastrzebski@qah.pl
Scientific contact	Deputy General Manager, QAH Sp. z o.o. Sp. k., +48 426563048, mateusz.jastrzebski@qah.pl

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	27 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To prove non-inferiority in terms of efficacy and safety of new formulation of combination of fluticasone propionate / salmeterol (125µg / 25µg) in MDI HFA inhaler applied two puffs twice daily compared with the reference drug at a dose of 500µg / 50µg in DPI (dry powder inhaler) type disc applied one puff twice daily in patients with chronic asthma.
Primary endpoint of the trial: avarage morning PEF during 12-week treatment period (change from Week1 to Week12)

Protection of trial subjects:

All patients were informed in details on the study procedures and their rights, all expressed in written their consent to participate in the trial. Due to the study design no further protection procedures were needed.

Background therapy:

All subjects were randomised to one of two study arms. During the study period subjects receive therapies due to their comorbidities (mostly: hypertension, diabetes mellitus, other respiratory conditions, gastrointestinal diseases).

Evidence for comparator:

The comparator used in the study contains the same molecules as the investigated drug, but at different doses. Additionally, they are administered from a different type of inhaler (DPI) that generates larger diameter particles and reaches the upper level of the respiratory tract. Administering a combination of fluticasone propionate and salmeterol from the DPI inhaler has been the standard way of administering these drugs so far.

Actual start date of recruitment	15 January 2018
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	Poland: 231
Worldwide total number of subjects	231
EEA total number of subjects	231

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)	199
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in one large University Hospital (Allergology Department) and 12 outpatient clinics. The first patient was recruited in March 2018, the last one in October 2019.

Pre-assignment

Screening details:

Patient screening was conducted according to the study inclusion criteria. At the screening visit laboratory tests were performed, and the patient was instructed on how to use the peak flow meter and recorded its indications in the patient's diary. During the screening visit, the current treatment of the patient did not change.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Comboterol

Arm description:

Subjects randomized to be treated with investigated drug - Comboterol.
Comboterol is a combination of salmeterol and fluticasone propionate inhaled using the MDI HFA inhaler. The investigated group will receive COMBOTEROL (25 µg / 125 µg) administered in the MDI HFA inhaler two doses twice a aday.

Arm type	Experimental
Investigational medicinal product name	Comboterol 25 µg / 125 µg
Investigational medicinal product code	R03AK06
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Comboterol, 25 µg + 125 µg (salmeterol + fluticasone propionate) / inhalation dose, inhalation aerosol, suspension - two doses twice a day.

Arm title	Seretide 500

Arm description:

Seretide Disk 500, 50 µg + 500 µg (salmeterol + fluticasone propionate) / inhalation dose, inhalation powder.
Seretide is a combination of salmeterol and fluticasone propionate inhaled using the DPI-Disk inhaler. It is a multi dose, flow dependent, medium resistance inhaler. Its optimal inspiratory flow is 30-60 l / min. At a flow of 30 liters, 80% of the dose reaches the patient's mouth from the inhaler. The pulmonary deposition of this inhaler is 11.9-16.6%

Arm type	Active comparator
Investigational medicinal product name	Seretide Dysk 500
Investigational medicinal product code	R03AK06
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Seretide Disk 500, 50 µg + 500 µg (salmeterol + fluticasone propionate) / inhalation dose, inhalation powder - twice a day, one dose each

Number of subjects in period 1	Comboterol	Seretide 500
Started	117	114
Completed	111	110
Not completed	6	4
Consent withdrawn by subject	2	1
Adverse event, non-fatal	2	3
Lost to follow-up	2	-

Period 2

Period 2 title	Overall Trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Comboterol

Arm description:

Subjects randomized to be treated with investigated drug - Comboterol.
Comboterol is a combination of salmeterol and fluticasone propionate inhaled using the MDI HFA inhaler. The investigated group will receive COMBOTEROL (25 µg / 125 µg) administered in the MDI HFA inhaler two doses twice a aday.

Arm type	Experimental
Investigational medicinal product name	Comboterol 25 µg / 125 µg
Investigational medicinal product code	R03AK06
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Comboterol, 25 µg + 125 µg (salmeterol + fluticasone propionate) / inhalation dose, inhalation aerosol, suspension - two doses twice a day.

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Arm description:

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Arm type	Active comparator

Investigational medicinal product name	Seretide Dysk 500
Investigational medicinal product code	R03AK06
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Seretide Disk 500, 50 µg + 500 µg (salmeterol + fluticasone propionate) / inhalation dose, inhalation powder - twice a day, one dose each

Number of subjects in period 2	Comboterol	Seretide 500
Started	117	114
Completed	111	110
Not completed	6	4
Consent withdrawn by subject	2	1
Adverse event, non-fatal	2	3
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	231	231	
Age categorical Units: Subjects			
Adults (18-64 years)	199	199	
From 65-84 years	32	32	
Age continuous Units: years			
median	49.5		
standard deviation	± 12.2	-	
Gender categorical Units: Subjects			
Female	138	138	
Male	93	93	

End points

End points reporting groups

Reporting group title	Comboterol

Reporting group description:

Subjects randomized to be treated with investigated drug - Comboterol.
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Primary: Mean morning PEF change

End point title	Mean morning PEF change

End point description:

End point type	Primary

End point timeframe:

Mean change in morning PEF over the 12-week treatment period. The baseline value will be calculated as the average of the 14 days of the screening period. The average PEF for visit 4 will be calculated from the last 14 days before the visit.

End point values	Comboterol	Seretide 500	Comboterol	Seretide 500
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	114	111	110
Units: l/s				
median (confidence interval 95%)	6.2 (5.8 to 6.5)	6.0 (5.7 to 6.4)	6.6 (6.2 to 7.1)	6.9 (6.4 to 7.3)

Attachments (see zip file)	COMBO_PEF.png

Statistical analyses

Statistical analysis title	Final

Statistical analysis description:

The results were analyzed with StatSoft Statistica 13 (StatSoft, Poland). To detect a 15 l/min difference in the morning PEF value between the two treatment groups (standard deviation [SD]=45 l/min, significance level 5%, power 80%), we used a sample size of 110 patients for each group. The patients' characteristics were compared using the chi-squared or Fisher's exact two-tailed test for discrete variables, or the Student's t-test for continuous variables.

Comparison groups	Comboterol v Seretide 500
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Asthma Control Test ACT

End point title	Asthma Control Test ACT

End point description:

End point type	Secondary

End point timeframe:

ACT change was measured based on the comparison of initial completion at Visit I and final observation at Visit IV.

End point values	Comboterol	Seretide 500	Comboterol	Seretide 500
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	114	111	110
Units: number				
number (confidence interval 95%)	18.7 (17.9 to 19.4)	18.7 (17.9 to 19.4)	20.7 (20.1 to 21.4)	20.5 (19.9 to 21.2)

Attachments (see zip file)	COMBO_ACT.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected after subject entry through the whole study participation of each study subject.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	MDI 250
Reporting group description: -	
Reporting group title	DPI 500

Reporting group description: -

Serious adverse events	MDI 250	DPI 500	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (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: 5 %

Non-serious adverse events	MDI 250	DPI 500	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 117 (87.18%)	104 / 114 (91.23%)	
Cardiac disorders			
ECG deviations			
subjects affected / exposed	8 / 117 (6.84%)	10 / 114 (8.77%)	
occurrences (all)	8	10	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 117 (1.71%)	2 / 114 (1.75%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Laboratory tests abnormalities			

subjects affected / exposed	95 / 117 (81.20%)	99 / 114 (86.84%)	
occurrences (all)	145	145	
Respiratory, thoracic and mediastinal disorders			
Hoarseness			
subjects affected / exposed	0 / 117 (0.00%)	5 / 114 (4.39%)	
occurrences (all)	0	5	
Infections and infestations			
Cold			
subjects affected / exposed	5 / 117 (4.27%)	5 / 114 (4.39%)	
occurrences (all)	5	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33276251