



## 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: average 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        |
| <b>Arm title</b>             | 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 day.

|  |                           |
|--|---------------------------|
| 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.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | 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         |
| <b>Arm title</b>             | 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 day.

|  |                           |
|--|---------------------------|
| 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.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 2</b> | Combaterol | 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:<br>Subjects randomized to be treated with investigated drug - Comboterol.<br>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 day.   |              |
| Reporting group title  | Seretide 500 |
| Reporting group description:<br>Seretide Disk 500, 50 µg + 500 µg (salmeterol + fluticasone propionate) / inhalation dose, inhalation powder.<br>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% |              |
| Reporting group title  | Comboterol   |
| Reporting group description:<br>Subjects randomized to be treated with investigated drug - Comboterol.<br>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 day.   |              |
| Reporting group title  | Seretide 500 |
| Reporting group description:<br>Seretide Disk 500, 50 µg + 500 µg (salmeterol + fluticasone propionate) / inhalation dose, inhalation powder.<br>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% |              |

### Primary: Mean morning PEF change

|   |                         |
|---|-------------------------|
| End point title   | Mean morning PEF change |
| End point description:  |                         |
| End point type  | Primary                 |
| End point timeframe:<br>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) |



|                                   |               |
|-----------------------------------|---------------|
| <b>Attachments (see zip file)</b> | COMBO_PEF.png |
|-----------------------------------|---------------|

## Statistical analyses

|                                   |       |
|-----------------------------------|-------|
| <b>Statistical analysis title</b> | 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                       | Combaterol 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.

| <b>End point values</b>          | Combaterol          | Seretide 500        | Combaterol          | 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) |

|                                   |               |
|-----------------------------------|---------------|
| <b>Attachments (see zip file)</b> | 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<br>occurrences (all)  | 95 / 117 (81.20%)<br>145 | 99 / 114 (86.84%)<br>145 |  |
| Respiratory, thoracic and mediastinal disorders<br>Hoarseness<br>subjects affected / exposed<br>occurrences (all) | 0 / 117 (0.00%)<br>0     | 5 / 114 (4.39%)<br>5     |  |
| Infections and infestations<br>Cold<br>subjects affected / exposed<br>occurrences (all)                           | 5 / 117 (4.27%)<br>5     | 5 / 114 (4.39%)<br>5     |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

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