



Clinical trial results:

A two-arm, randomised, assessor-blind, parallel group study to evaluate the effect of fluticasone/formoterol breath actuated inhaler (BAI) and Relvar Ellipta DPI on ventilation heterogeneity in subjects with partially controlled or uncontrolled asthma.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-000801-38 |
| Trial protocol | SE SK |
| Global end of trial date | 14 August 2017 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 16 August 2018 |
| First version publication date | 16 August 2018 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | KFL3502 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Mundipharma Research Ltd. |
| Sponsor organisation address | Cambridge Science Park, Cambridge, United Kingdom, CB4 0GW |
| Public contact | Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.com |
| Scientific contact | Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.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 | 14 August 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 August 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 August 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate improvement of peripheral airway resistance (R5-R20) from baseline with fluticasone/formoterol breath actuated inhaler (BAI).

Protection of trial subjects:

All subjects were provided with oral and written information describing the nature and duration of the study, its purpose, the procedures to be performed, the potential risks and benefits involved, and any potential discomfort. Each subject was given a copy of the PIS and ICF. The subject was asked to sign and date an ICF prior to any study-specific procedures being performed.

Background therapy:

Subjects already on Seretide Accuhaler 250/50 µg BID at screening underwent a run-in period of 2 weeks during which they continued their Seretide Accuhaler medication. Subjects on equivalent /higher doses of other ICS-LABAs or higher dose of Seretide at screening were also eligible to undergo a run-in of 4 weeks on Seretide Accuhaler 250/50 µg BID.

As well as receiving IMP, all subjects were also provided with Ventolin (salbutamol) as rescue medication at the start of the run-in period to be used as needed during the run in and treatment periods of the study at a dose of up to 8 puffs/day.

Evidence for comparator:

Relvar Ellipta was chosen as a comparator product because it is an approved ICS-LABA combination therapy. Relvar Ellipta is a dry powder inhaler (DPI).

| | |
|---|--------------|
| Actual start date of recruitment | 14 June 2016 |
| 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 | Australia: 10 |
| Country: Number of subjects enrolled | United Kingdom: 22 |
| Country: Number of subjects enrolled | New Zealand: 7 |
| Country: Number of subjects enrolled | Slovakia: 59 |
| Country: Number of subjects enrolled | Sweden: 5 |
| Worldwide total number of subjects | 103 |
| EEA total number of subjects | 86 |

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) | 85 |
| From 65 to 84 years | 17 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

This study was carried out at 5 sites in Australia, New Zealand, Slovakia, Sweden and the UK. The first subject first visit was carried out on 14 June 2016 and the last subject last visit was conducted on 14 Aug 2017.

Pre-assignment

Screening details:

240 subjects provided written informed consent and were screened. 103 subjects failed screening: 98 failed screening procedures, 2 withdrew, 2 failed due to administrative reasons, 1 failed due to AE. 34 subjects failed run-in: 2 due to administrative reasons, 2 failed due to AE, 1 was non-compliant and 29 did not meet randomisation criteria.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Assessor ^[1] |

Blinding implementation details:

Each investigator site had a named, unblinded person who dispensed run-in medication, rescue medication and IMP to subjects. This person was not involved in the assessment of subjects.

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Fluticasone/formoterol BAI |

Arm description:

Fluticasone/formoterol BAI, 125/5, 2 puffs, BID

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Fluticasone/formoterol BAI |
| Investigational medicinal product code | Fluticasone/formoterol BAI |
| Other name | |
| Pharmaceutical forms | Inhalation powder, Pressurised inhalation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

125/5 µg; 2 puffs, twice a day.

| | |
|------------------|----------------|
| Arm title | Relvar Ellipta |
|------------------|----------------|

Arm description:

Relvar Ellipta, 1 puff, BID

| | |
|--|----------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Fluticasone/vilanterol DPI |
| Investigational medicinal product code | Relvar Ellipta |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

92/22 µg; 1 puff, once a day.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The study was designed as assessor-blind due to the challenges associated with developing a placebo device for Relvar Ellipta. Nonetheless, because of the objective nature of the primary and key secondary efficacy variables, the subject's knowledge of their treatment was unlikely to influence the

key study outcomes. Furthermore, use of two different devices which require different inspiratory techniques may have created patient confusion leading to more handling errors.

| Number of subjects in period 1 | Fluticasone/formoterol BAI | Relvar Ellipta |
|---------------------------------------|----------------------------|----------------|
| Started | 54 | 49 |
| Completed | 51 | 49 |
| Not completed | 3 | 0 |
| Consent withdrawn by subject | 1 | - |
| Adverse event, non-fatal | 2 | - |

Baseline characteristics

Reporting groups

| | |
|---|----------------------------|
| Reporting group title | Fluticasone/formoterol BAI |
| Reporting group description: Fluticasone/formoterol BAI, 125/5, 2 puffs, BID | |
| Reporting group title | Relvar Ellipta |
| Reporting group description: Relvar Ellipta, 1 puff, BID | |

| Reporting group values | Fluticasone/formoterol BAI | Relvar Ellipta | Total |
|--|----------------------------|-------------------|-------|
| Number of subjects | 54 | 49 | 103 |
| Age categorical Units: Subjects | | | |
| Adults (18-65 years) | 45 | 40 | 85 |
| 66 years and over | 9 | 9 | 18 |
| Age continuous Units: years arithmetic mean standard deviation | 52.1 ± 12.65 | 52.8 ± 13.98 | - |
| Gender categorical Units: Subjects | | | |
| Female | 34 | 36 | 70 |
| Male | 20 | 13 | 33 |
| Race Units: Subjects | | | |
| White | 51 | 46 | 97 |
| Black or African American | 0 | 2 | 2 |
| Asian | 2 | 1 | 3 |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Other | 0 | 0 | 0 |
| Weight Units: kg arithmetic mean standard deviation | 85.25 ± 19.192 | 77.79 ± 16.035 | - |
| Height Units: cm arithmetic mean standard deviation | 166.5 ± 9.99 | 163.6 ± 7.51 | - |
| BMI Units: kg/m ² arithmetic mean standard deviation | 30.66 ± 6.038 | 29.10 ± 5.901 | - |

End points

End points reporting groups

| | |
|---|----------------------------|
| Reporting group title | Fluticasone/formoterol BAI |
| Reporting group description: Fluticasone/formoterol BAI, 125/5, 2 puffs, BID | |
| Reporting group title | Relvar Ellipta |
| Reporting group description: Relvar Ellipta, 1 puff, BID | |

Primary: Change in R5-R20 (peripheral airway resistance) from baseline to week 8

| | |
|---|---|
| End point title | Change in R5-R20 (peripheral airway resistance) from baseline to week 8 |
| End point description: Peripheral airway resistance (R5-R20) was measured by Impulse Oscillometry as the difference between total airway resistance (R5) and central airway resistance (R20) | |
| End point type | Primary |
| End point timeframe: From baseline to week 8. | |

| End point values | Fluticasone/formoterol BAI | Relvar Ellipta | | |
|--|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 | 49 | | |
| Units: kPa/L/s | | | | |
| least squares mean (confidence interval 95%) | 0.01 (-0.026 to 0.039) | -0.02 (-0.059 to 0.013) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Fluticasone/Formoterol vs Relvar Ellipta |
| Statistical analysis description: Statistical analysis was done using a mixed-model repeated measures (MMRM) analysis of covariance (ANCOVA) with fixed terms for treatment group, visit, treatment*visit interaction, ICS/LABA use at screening (Seretide Accuhaler 250/50 µg BID; other ICS/LABA at Seretide Accuhaler 250/50 µg BID-equivalents; other ICS/LABA or Seretide Accuhaler at dose > Seretide Accuhaler 250/50 µg BID-equivalents) and baseline R5-R20 as a covariate. Multiple Imputation (MI) was employed to account for missing data | |
| Comparison groups | Fluticasone/formoterol BAI v Relvar Ellipta |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.172 ^[1] |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | 0.03 |

| Confidence interval | |
|---------------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.013 |
| upper limit | 0.072 |

Notes:

[1] - The primary comparison was change from baseline to week 8.

p=0.693 for the LS mean difference from baseline to week 8 for Fluticasone/Formoterol BAI group.

p=0.210 for the LS mean difference from baseline to week 8 for Relvar Ellipta.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events were recorded from the point at which the Informed Consent was signed until 14 days after the subject left the study. This included new AEs that were reported in the 14 days following the subject's completion/discontinuation visit.

Adverse event reporting additional description:

Only treatment emergent AEs were analysed. A treatment emergent AE was defined as any AE with an onset date on or after the first dose of IMP if the AE was absent before the first dose of IMP, or worsened after the first dose of IMP. This also included AEs with an onset date up to and including 7 days after the last dose of IMP.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Fluticasone/formoterol BAI |
|-----------------------|----------------------------|

Reporting group description:

Fluticasone/formoterol BAI, 125/5, 2 puffs, BID

| | |
|-----------------------|----------------|
| Reporting group title | Relvar Ellipta |
|-----------------------|----------------|

Reporting group description:

Relvar Ellipta, 1 puff, BID

| Serious adverse events | Fluticasone/formoterol BAI | Relvar Ellipta | |
|---|----------------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 1 / 49 (2.04%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Liver disorder | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Asthma | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 49 (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: 1 %

| Non-serious adverse events | Fluticasone/formoterol BAI | Relvar Ellipta | |
|---|----------------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 54 (40.74%) | 11 / 49 (22.45%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Squamous cell carcinoma of head and neck | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 49 (2.04%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 49 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Humidity intolerance | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 49 (2.04%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 49 (2.04%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 1 / 49 (2.04%) | |
| occurrences (all) | 5 | 1 | |

| | | | |
|---|---------------------|---------------------|--|
| Cough subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 49 (2.04%) 1 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Haemoptysis subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 49 (2.04%) 1 | |
| Nasal polyps subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 49 (2.04%) 1 | |
| Blood cholesterol increased subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Blood triglycerides increased subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 0 / 49 (0.00%) 0 | |
| Lymphocyte count increased subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 2 | 0 / 49 (0.00%) 0 | |
| Injury, poisoning and procedural complications Hand fracture subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Limb injury subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Nervous system disorders | | | |

| | | | |
|--|--|--|--|
| Carpal tunnel syndrome subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 49 (2.04%) 1 | |
| VIIth nerve paralysis subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Blood and lymphatic system disorders Lymphadenitis subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Ear and labyrinth disorders Vertigo positional subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 3 1 / 54 (1.85%) 1 0 / 54 (0.00%) 0 1 / 54 (1.85%) 2 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 1 / 49 (2.04%) 1 0 / 49 (0.00%) 0 | |
| Hepatobiliary disorders Liver disorder subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all) Urticaria | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Spinal pain subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 3 | 2 / 49 (4.08%) 2 | |
| Rhinitis subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 1 / 49 (2.04%) 1 | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 1 / 49 (2.04%) 1 | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 1 / 49 (2.04%) 1 | |
| Gastroenteritis viral subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 49 (2.04%) 1 | |
| Laryngitis subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Pharyngitis subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 49 (0.00%) 0 | |
| Respiratory tract infection | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 49 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 49 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 29 April 2016 | Protocol Amendment No. 1 was required to remove Functional Respiratory Imaging (FRI) as a secondary objective from the protocol. The HDCT scans at Visits 2, 4, 5 and the associated endpoints and analyses were removed from the protocol. This amendment was implemented as the risk:benefit ratio for exposing subjects recruited under this protocol to radiation associated with HDCT scans was considered unfavourable. This decision was made following review of the study protocol by the UK research ethics committee (Cambridge East Research Ethics Committee). |
| 05 January 2017 | Protocol Amendment No. 2 was intended to address recruitment challenges in the study without detriment to the scientific quality of the study. The current recruitment rate had been significantly slower than anticipated and this amendment was intended to address the issues which were found to be impacting on this; in this amendment the screening and randomisation inclusion value of IOS R5-R20 were lowered, a second IOS was allowed at screening to mitigate issues associated with subjects failing to withhold medication per the protocol instructions, and the sample size was reduced. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported