



## Clinical trial results:

### A guideline approach to therapy step-down utilising Flutiform®: change and step-down (FFLU-X study)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2013-005365-39   |
| Trial protocol           | GB               |
| Global end of trial date | 26 February 2016 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 26 January 2021 |
| First version publication date | 26 January 2021 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | OR00213 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |            |
|------------------------------------|------------|
| ISRCTN number                      | -          |
| ClinicalTrials.gov id (NCT number) | -          |
| WHO universal trial number (UTN)   | -          |
| Other trial identifiers            | PCRN: 2942 |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Research in Real-Life   |
| Sponsor organisation address | 5 Coles Lane, Cambridge, United Kingdom,                                |
| Public contact               | Anu Kemppinen, Research in Real-Life Ltd, +44 01223967886, anu@rirl.org |
| Scientific contact           | Anu Kemppinen, Research in Real-Life Ltd, +44 01223967886, anu@rirl.org |

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                       | 17 March 2016    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 26 February 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 26 February 2016 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

This study has two phases. The primary objective of each phase is as follows:

Phase 1: to test effectiveness of a recently licensed inhaler treatment, Flutiform®, against the effectiveness of a commonly used Seretide® Evohaler® inhaler in controlling asthma in real-life patients.

Phase 2: to test if asthma control can be maintained with a reduced dosage of Flutiform®

Protection of trial subjects:

Routine care

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 03 March 2014 |
| 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 | United Kingdom: 225 |
| Worldwide total number of subjects   | 225                 |
| EEA total number of subjects         | 0                   |

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)                      | 164 |
| From 65 to 84 years                       | 61  |



## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited at 29 National Health Service (NHS) primary care centres across England. Recruitment period was 1 July 2014-26 February 2016.

### Pre-assignment

Screening details:

A total of 259 patients with asthma were screened. Of these, 225 patients at 27 centres in the UK were randomised 2:1 into Phase 1, 151 patients to FP/FOR(1000) and 74 patients to FP/SAL(1000)] (Figure 3). A total of 34 patients were not enrolled because of screening failure.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Phase 1                     |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | FP/FOR(1000) |

Arm description:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250)

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Flutiform® 250      |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | FP/SAL(1000) |
|------------------|--------------|

Arm description:

Fluticasone Propionate/Salmeterol Xinafoate 250µg/25µg 2 puffs twice daily (as Seretide® 250 Evohaler®)

|  |                         |
|--|-------------------------|
| Arm type                               | Active comparator       |
| Investigational medicinal product name | Seretide® 250 Evohaler® |
| Investigational medicinal product code |                         |
| Other name                             |                         |
| Pharmaceutical forms                   | Inhalation solution     |
| Routes of administration               | Inhalation use          |

Dosage and administration details:

Fluticasone Propionate/Salmeterol Xinafoate 250µg/25µg 2 puffs twice daily

| <b>Number of subjects in period 1</b> | FP/FOR(1000) | FP/SAL(1000) |
|---------------------------------------|--------------|--------------|
| Started                               | 151          | 74           |
| Completed                             | 134          | 73           |
| Not completed                         | 17           | 1            |
| Consent withdrawn by subject          | 1            | -            |
| not recorded                          | 2            | -            |
| Adverse event, non-fatal              | 7            | -            |
| Lost to follow-up                     | 6            | 1            |
| Protocol deviation                    | 1            | -            |

## Period 2

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | Phase 2                     |
| Is this the baseline period? | No                          |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | FP/FOR(1000) |

Arm description:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250)

|  |                     |
|--|---------------------|
| Arm type                               | Active comparator   |
| Investigational medicinal product name | Flutiform® 250      |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | FP/FOR(500) |
|------------------|-------------|

Arm description:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 125µg/5µg 2 puffs twice daily (as Flutiform® 125)

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | FP/FOR(500)         |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 125µg/5µg 2 puffs twice daily (as Flutiform® 125)

| <b>Number of subjects in period 2<sup>[1]</sup></b> | FP/FOR(1000) | FP/FOR(500) |
|---|--------------|-------------|
| Started   | 58           | 58          |
| Completed   | 54           | 53          |
| Not completed                                       | 4            | 5           |
| Adverse event, serious fatal                        | -            | 1           |
| not recorded  | 1            | -           |
| Adverse event, non-fatal                            | 1            | -           |
| Lost to follow-up                                   | 2            | 4           |

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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Eighteen of the 134 patients completing Phase 1 in the FP/FOR(1000) group were not randomised into Phase 2 because they did not meet the criteria for Phase 2.

## Baseline characteristics

### Reporting groups

|   |              |
|---|--------------|
| Reporting group title   | FP/FOR(1000) |
| Reporting group description:<br>Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250) |              |

|   |              |
|---|--------------|
| Reporting group title   | FP/SAL(1000) |
| Reporting group description:<br>Fluticasone Propionate/Salmeterol Xinafoate 250µg/25µg 2 puffs twice daily (as Seretide® 250 Evohaler®) |              |

| Reporting group values                             | FP/FOR(1000) | FP/SAL(1000) | Total |
|--|--------------|--------------|-------|
| Number of subjects                                 | 151          | 74           | 225   |
| 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)                               |              |              | 0     |
| From 65-84 years                                   |              |              | 0     |
| 85 years and over                                  |              |              | 0     |
| Age continuous                                     |              |              |       |
| Units: years                                       |              |              |       |
| arithmetic mean                                    | 53.0         | 55.1         |       |
| standard deviation                                 | ± 13.4       | ± 13.7       | -     |
| Gender categorical                                 |              |              |       |
| Units: Subjects                                    |              |              |       |
| Female   | 82           | 43           | 125   |
| Male   | 69           | 31           | 100   |

## End points

### End points reporting groups

|                              |   |
|------------------------------|---|
| Reporting group title        | FP/FOR(1000)  |
| Reporting group description: | Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250) |
| Reporting group title        | FP/SAL(1000)  |
| Reporting group description: | Fluticasone Propionate/Salmeterol Xinafoate 250µg/25µg 2 puffs twice daily (as Seretide® 250 Evohaler®) |
| Reporting group title        | FP/FOR(1000)  |
| Reporting group description: | Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250) |
| Reporting group title        | FP/FOR(500)   |
| Reporting group description: | Fluticasone Propionate/Formoterol Fumarate Dihydrate 125µg/5µg 2 puffs twice daily (as Flutiform® 125)  |

### Primary: ACQ7

|                        |   |
|------------------------|---|
| End point title        | ACQ7                                    |
| End point description: | 7-question Asthma Control Questionnaire |
| End point type         | Primary                                 |
| End point timeframe:   | 12 weeks                                |

| End point values                     | FP/FOR(1000)    | FP/SAL(1000)    | FP/FOR(1000)    | FP/FOR(500)     |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 125             | 72              | 52              | 52              |
| Units: score                         |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 0.7 (± 0.8)     | 0.8 (± 0.8)     | 0.7 (± 0.8)     | 0.8 (± 0.8)     |

### Statistical analyses

|                            |                             |
|----------------------------|-----------------------------|
| Statistical analysis title | Non-inferiority Phase 1     |
| Comparison groups          | FP/FOR(1000) v FP/SAL(1000) |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 197             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Odds ratio (OR) |
| Point estimate                          | -0.12           |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | -0.32           |
| upper limit                             | 0.09            |

|   |                            |  |  |  |
|---|----------------------------|--|--|--|
| <b>Statistical analysis title</b>       | Non-inferiority Phase 2    |  |  |  |
| Comparison groups                       | FP/FOR(500) v FP/FOR(1000) |  |  |  |
| Number of subjects included in analysis | 104                        |  |  |  |
| Analysis specification                  | Pre-specified              |  |  |  |
| Analysis type                           | non-inferiority            |  |  |  |
| Parameter estimate                      | Odds ratio (OR)            |  |  |  |
| Point estimate                          | 0.01                       |  |  |  |
| Confidence interval                     |                            |  |  |  |
| level                                   | 95 %                       |  |  |  |
| sides                                   | 2-sided                    |  |  |  |
| lower limit                             | -0.2                       |  |  |  |
| upper limit                             | 0.22                       |  |  |  |

### Secondary: Mini-AQLQ

|                        |           |
|------------------------|-----------|
| End point title        | Mini-AQLQ |
| End point description: |           |
| End point type         | Secondary |
| End point timeframe:   |           |
| 12 weeks               |           |

| <b>End point values</b>          | FP/FOR(1000)    | FP/SAL(1000)    | FP/FOR(1000)    | FP/FOR(500)     |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type               | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed      | 133             | 73              | 54              | 53              |
| Units: Score                     |                 |                 |                 |                 |
| arithmetic mean (standard error) | 6.1 (± 1.1)     | 5.8 (± 1.1)     | 6.3 (± 0.9)     | 6.2 (± 1.1)     |

### Statistical analyses

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Mini-AQLQ Phase 1           |
| Comparison groups                       | FP/FOR(1000) v FP/SAL(1000) |
| Number of subjects included in analysis | 206                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | non-inferiority             |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 0.24                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -0.05                       |
| upper limit                             | 0.53                        |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Mini-AQLQ Phase 2          |
| Comparison groups                       | FP/FOR(500) v FP/FOR(1000) |
| Number of subjects included in analysis | 107                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           |                            |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | -0.04                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.31                      |
| upper limit                             | 0.24                       |

### Secondary: GINA

|   |           |
|---|-----------|
| End point title   | GINA      |
| End point description:<br>Asthma control according to Global Initiative for Asthma (GINA) |           |
| End point type  | Secondary |
| End point timeframe:<br>12 weeks  |           |

| <b>End point values</b>     | FP/FOR(1000)    | FP/SAL(1000)    | FP/FOR(1000)    | FP/FOR(500)     |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 124             | 73              | 54              | 53              |
| Units: number of patients   |                 |                 |                 |                 |
| Controlled                  | 71              | 28              | 30              | 26              |
| Partially controlled        | 53              | 33              | 15              | 19              |
| Uncontrolled                | 10              | 12              | 9               | 8               |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Phase 1 (12 weeks) and Phase 2 (12 weeks)

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Phase 1 FP/FOR(1000) |
|-----------------------|----------------------|

Reporting group description: -

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Phase 1 FP/SAL(1000) |
|-----------------------|----------------------|

Reporting group description: -

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Phase 2 FP/FOR(500) |
|-----------------------|---------------------|

Reporting group description: -

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Phase 2 FP/FOR(1000) |
|-----------------------|----------------------|

Reporting group description: -

| <b>Serious adverse events</b>                        | Phase 1<br>FP/FOR(1000) | Phase 1<br>FP/SAL(1000) | Phase 2<br>FP/FOR(500) |
|--|-------------------------|-------------------------|------------------------|
| Total subjects affected by serious adverse events    |                         |                         |                        |
| subjects affected / exposed                          | 0 / 151 (0.00%)         | 2 / 74 (2.70%)          | 2 / 58 (3.45%)         |
| number of deaths (all causes)                        | 0                       | 0                       | 1                      |
| number of deaths resulting from adverse events       | 0                       | 0                       | 1                      |
| Injury, poisoning and procedural complications       |                         |                         |                        |
| Intentional self-injury                              |                         |                         |                        |
| subjects affected / exposed                          | 0 / 151 (0.00%)         | 1 / 74 (1.35%)          | 0 / 58 (0.00%)         |
| occurrences causally related to treatment / all      | 0 / 0                   | 0 / 1                   | 0 / 0                  |
| deaths causally related to treatment / all           | 0 / 0                   | 0 / 0                   | 0 / 0                  |
| General disorders and administration site conditions |                         |                         |                        |
| Death  |                         |                         |                        |
| subjects affected / exposed                          | 0 / 151 (0.00%)         | 0 / 74 (0.00%)          | 1 / 58 (1.72%)         |
| occurrences causally related to treatment / all      | 0 / 0                   | 0 / 0                   | 0 / 1                  |
| deaths causally related to treatment / all           | 0 / 0                   | 0 / 0                   | 0 / 1                  |
| Respiratory, thoracic and mediastinal disorders      |                         |                         |                        |
| Pneumonia bacterial                                  |                         |                         |                        |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 151 (0.00%) | 1 / 74 (1.35%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Lower respiratory tract infection               |                 |                |                |
| subjects affected / exposed                     | 0 / 151 (0.00%) | 0 / 74 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                        | Phase 2<br>FP/FOR(1000) |  |  |
|--|-------------------------|--|--|
| Total subjects affected by serious adverse events    |                         |  |  |
| subjects affected / exposed                          | 0 / 58 (0.00%)          |  |  |
| number of deaths (all causes)                        | 0                       |  |  |
| number of deaths resulting from adverse events       | 0                       |  |  |
| Injury, poisoning and procedural complications       |                         |  |  |
| Intentional self-injury                              |                         |  |  |
| subjects affected / exposed                          | 0 / 58 (0.00%)          |  |  |
| occurrences causally related to treatment / all      | 0 / 0                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                   |  |  |
| General disorders and administration site conditions |                         |  |  |
| Death  |                         |  |  |
| subjects affected / exposed                          | 0 / 58 (0.00%)          |  |  |
| occurrences causally related to treatment / all      | 0 / 0                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                   |  |  |
| Respiratory, thoracic and mediastinal disorders      |                         |  |  |
| Pneumonia bacterial                                  |                         |  |  |
| subjects affected / exposed                          | 0 / 58 (0.00%)          |  |  |
| occurrences causally related to treatment / all      | 0 / 0                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                   |  |  |
| Lower respiratory tract infection                    |                         |  |  |
| subjects affected / exposed                          | 0 / 58 (0.00%)          |  |  |
| occurrences causally related to treatment / all      | 0 / 0                   |  |  |
| deaths causally related to treatment / all           | 0 / 0                   |  |  |

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

| <b>Non-serious adverse events</b>                     | Phase 1<br>FP/FOR(1000) | Phase 1<br>FP/SAL(1000) | Phase 2<br>FP/FOR(500) |
|---|-------------------------|-------------------------|------------------------|
| Total subjects affected by non-serious adverse events |                         |                         |                        |
| subjects affected / exposed                           | 34 / 151 (22.52%)       | 21 / 74 (28.38%)        | 34 / 58 (58.62%)       |
| Respiratory, thoracic and mediastinal disorders       |                         |                         |                        |
| Nasopharyngitis                                       |                         |                         |                        |
| subjects affected / exposed                           | 9 / 151 (5.96%)         | 4 / 74 (5.41%)          | 12 / 58 (20.69%)       |
| occurrences (all)                                     | 9                       | 4                       | 13                     |
| Oropharyngeal pain                                    |                         |                         |                        |
| subjects affected / exposed                           | 6 / 151 (3.97%)         | 1 / 74 (1.35%)          | 4 / 58 (6.90%)         |
| occurrences (all)                                     | 7                       | 1                       | 4                      |
| Cough   |                         |                         |                        |
| subjects affected / exposed                           | 7 / 151 (4.64%)         | 5 / 74 (6.76%)          | 6 / 58 (10.34%)        |
| occurrences (all)                                     | 7                       | 5                       | 6                      |
| Lower respiratory tract infection                     |                         |                         |                        |
| subjects affected / exposed                           | 5 / 151 (3.31%)         | 4 / 74 (5.41%)          | 6 / 58 (10.34%)        |
| occurrences (all)                                     | 5                       | 4                       | 6                      |
| Productive cough                                      |                         |                         |                        |
| subjects affected / exposed                           | 1 / 151 (0.66%)         | 2 / 74 (2.70%)          | 3 / 58 (5.17%)         |
| occurrences (all)                                     | 1                       | 2                       | 3                      |
| Asthma  |                         |                         |                        |
| subjects affected / exposed                           | 5 / 151 (3.31%)         | 4 / 74 (5.41%)          | 4 / 58 (6.90%)         |
| occurrences (all)                                     | 5                       | 4                       | 4                      |
| Musculoskeletal and connective tissue disorders       |                         |                         |                        |
| Arthralgia  |                         |                         |                        |
| subjects affected / exposed                           | 2 / 151 (1.32%)         | 1 / 74 (1.35%)          | 3 / 58 (5.17%)         |
| occurrences (all)                                     | 2                       | 1                       | 3                      |
| Infections and infestations                           |                         |                         |                        |
| Urinary tract infection                               |                         |                         |                        |
| subjects affected / exposed                           | 3 / 151 (1.99%)         | 2 / 74 (2.70%)          | 4 / 58 (6.90%)         |
| occurrences (all)                                     | 3                       | 2                       | 4                      |

| <b>Non-serious adverse events</b>                     | Phase 2<br>FP/FOR(1000) |  |  |
|---|-------------------------|--|--|
| Total subjects affected by non-serious adverse events |                         |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 29 / 58 (50.00%) |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Nasopharyngitis                                 |                  |  |  |
| subjects affected / exposed                     | 15 / 58 (25.86%) |  |  |
| occurrences (all)                               | 17               |  |  |
| Oropharyngeal pain                              |                  |  |  |
| subjects affected / exposed                     | 3 / 58 (5.17%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Cough   |                  |  |  |
| subjects affected / exposed                     | 6 / 58 (10.34%)  |  |  |
| occurrences (all)                               | 6                |  |  |
| Lower respiratory tract infection               |                  |  |  |
| subjects affected / exposed                     | 6 / 58 (10.34%)  |  |  |
| occurrences (all)                               | 7                |  |  |
| Productive cough                                |                  |  |  |
| subjects affected / exposed                     | 4 / 58 (6.90%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Asthma  |                  |  |  |
| subjects affected / exposed                     | 4 / 58 (6.90%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Arthralgia                                      |                  |  |  |
| subjects affected / exposed                     | 2 / 58 (3.45%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Infections and infestations                     |                  |  |  |
| Urinary tract infection                         |                  |  |  |
| subjects affected / exposed                     | 1 / 58 (1.72%)   |  |  |
| occurrences (all)                               | 1                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 28 January 2014  | <p>Substantial Amendment 1 (dated 28 January 2014) to the protocol was issued before any patient was enrolled into the study. The amendments were as follows:</p> <ul style="list-style-type: none"><li>- The requirement for patients to have had at least 4 prescriptions of Seretide® 250 Evohaler® in the last 6 months before screening was removed; it was only required that the patient be on Seretide® 250 Evohaler® for the last 6 months before screening. The minimum number of prescriptions was initially set to at least 4 with the aim of ensuring adherence to treatment prior to study. However, this was removed given that the number of inhalers prescribed is unlikely to be a very accurate estimator of adherence.</li><li>- Inclusion criteria "Step 4 of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines" was removed as patients who are on Seretide® 250 Evohaler® are by definition at Step 4.</li><li>- While ACQ7&lt;1.5 was not listed in the inclusion criteria, this criterion was erroneously mentioned elsewhere in the protocol text and was removed to be consistent with the inclusion criteria listed.</li><li>- In Appendix C: "Actuation not corresponding with inhalation; actuation before inhalation or too late after inhalation (more than 2 seconds)" was erroneously listed as an error when using a spacer. This has been corrected.</li><li>- For randomisation to both Phase 1 and Phase 2, number of exacerbations in the 12 months prior to Phase 1 was considered; in the protocol version 1.0, it was erroneously stated that, for Phase 2 randomisation, the number of exacerbations in the 12 months before Phase 2 would be considered.</li></ul> |
| 17 November 2014 | <p>Substantial Amendment 2 (dated 17 November 2014) to the protocol was issued after 23 patients had been enrolled into the study. It included both substantial and non-substantial changes to the protocol, as follows:</p> <ul style="list-style-type: none"><li>- Substantial amendment to increase compensation to patients from £20 to £25/visit</li><li>- Non-substantial change of wording from "nurse" to "healthcare professional" in protocol and other relevant study documents to reflect that both nurses and pharmacists were recruiting patients and conducting clinics for the study</li><li>- A dedicated phone-line and website was set up for patients to express interest</li></ul> <p>There was no impact on the patients already enrolled into the study and this Amendment did not result in any changes that would impact outcomes or analyses of data.</p>   |

Notes:

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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/28351782>