



## Clinical trial results:

**A 12 Week, Randomized, Open-Label, Parallel Group Study to Evaluate the Mastery of Inhaler Technique for Budesonide Formoterol (BF) Spiromax(160/4.5 and 320/9 mcg) as Compared to SYMBICORT® TURBOHALER® (200/6 and 400/12 mcg) as Treatment for Adult Patients with Asthma (the Easy Low Instruction Over Time [ELIOT] Study)**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-004630-14 |
| Trial protocol           | GB             |
| Global end of trial date | 13 March 2015  |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 13 May 2017  |
| First version publication date | 13 May 2017  |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | BFS-AS-40035 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02062463 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                               |
|------------------------------|-----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Teva Branded Pharmaceutical Products R&D, Inc.                                                |
| Sponsor organisation address | 41 Moores Road, Frazer, Pennsylvania, United States, 19355                                    |
| Public contact               | Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 215 591 3000, |
| Scientific contact           | Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 215 591 3000, |

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                       | 15 October 2015 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 13 March 2015   |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

This is a 2-stage study. The primary objectives of the study are as follows:

- Stage 1: to determine the proportion of subjects achieving device mastery by the end of Step 3 of a 6-step standardized device training protocol for empty SPIROMAX is superior to empty TURBOHALER devices. Device mastery is defined as absence of nurse-observed errors.

- Stage 2: to determine whether the proportion of subjects maintaining device mastery, in subjects receiving inhaled corticosteroids/long-acting beta agonists (ICS/LABA) via BF SPIROMAX, is superior to ICS/LABA received via SYMBICORT TURBOHALER. Maintenance of device mastery is defined as absence of nurse-observed errors after 12 weeks of device use.

Protection of trial subjects:

For adult subjects, written informed consent signed and dated by the subject before conducting any study-related procedures; for minor subjects, written informed consent signed and dated by the parent/legal guardian and written assent signed and dated by the subject before conducting any study related procedure.

Background therapy: -

Evidence for comparator: -

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 28 May 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: 540 |
| Worldwide total number of subjects   | 540                 |
| EEA total number of subjects         | 540                 |

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)                     | 390 |
| From 65 to 84 years                      | 150 |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 540 patients with asthma were screened for enrollment into stage 1 of this study and 485 were enrolled.

### Period 1

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

### Arms

|                              |                                             |
|------------------------------|---------------------------------------------|
| Are arms mutually exclusive? | No                                          |
| <b>Arm title</b>             | Empty SPIROMAX Followed by Empty TURBOHALER |

Arm description:

Subjects were randomly assigned to training with empty SPIROMAX followed by empty SYMBICORT TURBOHALER devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.

|                                        |                                           |
|----------------------------------------|-------------------------------------------|
| Arm type                               | Empty device                              |
| Investigational medicinal product name | Empty Budesonide/Formoterol (BF) SPIROMAX |
| Investigational medicinal product code |                                           |
| Other name                             |                                           |
| Pharmaceutical forms                   | Inhalation powder                         |
| Routes of administration               | Inhalation use                            |

Dosage and administration details:

Subjects were educated on the device using empty training devices containing no active drug and no excipients.

|                                        |                            |
|----------------------------------------|----------------------------|
| Investigational medicinal product name | Empty SYMBICORT TURBOHALER |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Inhalation powder          |
| Routes of administration               | Inhalation use             |

Dosage and administration details:

Subjects were educated on the device using empty training devices containing no active drug excipients.

|                  |                                             |
|------------------|---------------------------------------------|
| <b>Arm title</b> | Empty TURBOHALER Followed by Empty SPIROMAX |
|------------------|---------------------------------------------|

Arm description:

Subjects were randomly assigned to training with empty SYMBICORT TURBOHALER followed by empty SPIROMAX devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.

|                                        |                            |
|----------------------------------------|----------------------------|
| Arm type                               | Empty device               |
| Investigational medicinal product name | Empty SYMBICORT TURBOHALER |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Inhalation powder          |
| Routes of administration               | Inhalation use             |

Dosage and administration details:

Subjects were educated on the device using empty training devices containing no active drug excipients.

|                                        |                                           |
|----------------------------------------|-------------------------------------------|
| Investigational medicinal product name | Empty Budesonide/Formoterol (BF) SPIROMAX |
| Investigational medicinal product code |                                           |
| Other name                             |                                           |
| Pharmaceutical forms                   | Inhalation powder                         |
| Routes of administration               | Inhalation use                            |

Dosage and administration details:

Subjects were educated on the device using empty training devices containing no active drug and no excipients.

| Number of subjects in period 1    | Empty SPIROMAX<br>Followed by Empty<br>TURBOHALER | Empty TURBOHALER<br>Followed by Empty<br>SPIROMAX |
|-----------------------------------|---------------------------------------------------|---------------------------------------------------|
| Started                           | 243                                               | 242                                               |
| Completed                         | 240                                               | 241                                               |
| Not completed                     | 3                                                 | 1                                                 |
| Consent withdrawn by subject      | 1                                                 | -                                                 |
| Reason not collected per protocol | 2                                                 | 1                                                 |

## Period 2

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

## Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | BF SPIROMAX |

Arm description:

ICS/LABA via the BF SPIROMAX device for 12 weeks of therapy.

|                                        |                                          |
|----------------------------------------|------------------------------------------|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Budesonide/Formoterol (BF) SPIROMAX      |
| Investigational medicinal product code |                                          |
| Other name                             | budesonide/formoterol fumarate dihydrate |
| Pharmaceutical forms                   | Inhalation powder                        |
| Routes of administration               | Inhalation use                           |

Dosage and administration details:

The doses in stage 2 were equivalent to that received via the subject's current device at baseline. Subjects who had had been receiving 800 to 1000 µg beclometasone-equivalent ICS per day were randomly assigned to receive 2 doses of budesonide/formoterol twice daily using the BF SPIROMAX 160/4.5 µg device. Subjects who had been receiving 1600 to 2000 µg beclometasone-equivalent ICS per day were randomly assigned to receive 2 doses of budesonide/formoterol twice daily using the BF SPIROMAX 320/9 µg device.

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

Arm description:

ICS/LABA via the SYMBICORT TURBOHALER device for 12 weeks of therapy.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|                                        |                      |
|----------------------------------------|----------------------|
| Investigational medicinal product name | SYMBICORT TURBOHALER |
| Investigational medicinal product code |                      |
| Other name                             |                      |
| Pharmaceutical forms                   | Inhalation powder    |
| Routes of administration               | Inhalation use       |

Dosage and administration details:

The doses in stage 2 were equivalent to that received via the subject's current device at baseline. Subjects who had had been receiving 800 to 1000 µg beclometasone-equivalent ICS per day were randomly assigned to receive 2 doses of budesonide/formoterol twice daily using the SYMBICORT TURBOHALER 200/6 µg device. Subjects who had been receiving 1600 to 2000 µg beclometasone equivalent ICS per day were randomly assigned to receive 2 doses of budesonide/formoterol twice daily using the SYMBICORT TURBOHALER 400/12 µg device.

| <b>Number of subjects in period 2</b> | <b>BF SPIROMAX</b> | <b>SYMBICORT TURBOHALER</b> |
|---------------------------------------|--------------------|-----------------------------|
| Started                               | 197                | 197                         |
| Completed                             | 144                | 141                         |
| Not completed                         | 53                 | 56                          |
| Consent withdrawn by subject          | 15                 | 10                          |
| Not specified                         | 3                  | 1                           |
| Adverse event                         | 12                 | 20                          |
| Non-compliance                        | -                  | 1                           |
| Lost to follow-up                     | 20                 | 20                          |
| Lack of efficacy                      | 3                  | 4                           |

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

|                       |                                             |
|-----------------------|---------------------------------------------|
| Reporting group title | Empty SPIROMAX Followed by Empty TURBOHALER |
|-----------------------|---------------------------------------------|

Reporting group description:

Subjects were randomly assigned to training with empty SPIROMAX followed by empty SYMBICORT TURBOHALER devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.

|                       |                                             |
|-----------------------|---------------------------------------------|
| Reporting group title | Empty TURBOHALER Followed by Empty SPIROMAX |
|-----------------------|---------------------------------------------|

Reporting group description:

Subjects were randomly assigned to training with empty SYMBICORT TURBOHALER followed by empty SPIROMAX devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: 485 of the enrolled subjects were randomized and entered Stage 1.

| Reporting group values             | Empty SPIROMAX<br>Followed by Empty<br>TURBOHALER | Empty TURBOHALER<br>Followed by Empty<br>SPIROMAX | Total |
|------------------------------------|---------------------------------------------------|---------------------------------------------------|-------|
| Number of subjects                 | 243                                               | 242                                               | 485   |
| Age categorical<br>Units: Subjects |                                                   |                                                   |       |

|                                                                         |                |                |     |
|-------------------------------------------------------------------------|----------------|----------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 54.4<br>± 13.8 | 53.1<br>± 14.2 | -   |
| Gender categorical<br>Units: Subjects                                   |                |                |     |
| Female                                                                  | 152            | 134            | 286 |
| Male                                                                    | 91             | 108            | 199 |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                 |                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                           | Empty SPIROMAX Followed by Empty TURBOHALER     |
| Reporting group description:<br>Subjects were randomly assigned to training with empty SPIROMAX followed by empty SYMBICORT TURBOHALER devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients. |                                                 |
| Reporting group title                                                                                                                                                                                                                                           | Empty TURBOHALER Followed by Empty SPIROMAX     |
| Reporting group description:<br>Subjects were randomly assigned to training with empty SYMBICORT TURBOHALER followed by empty SPIROMAX devices. Subjects were educated on each device using empty training devices containing no active drug and no excipients. |                                                 |
| Reporting group title                                                                                                                                                                                                                                           | BF SPIROMAX                                     |
| Reporting group description:<br>ICS/LABA via the BF SPIROMAX device for 12 weeks of therapy.                                                                                                                                                                    |                                                 |
| Reporting group title                                                                                                                                                                                                                                           | SYMBICORT TURBOHALER                            |
| Reporting group description:<br>ICS/LABA via the SYMBICORT TURBOHALER device for 12 weeks of therapy.                                                                                                                                                           |                                                 |
| Subject analysis set title                                                                                                                                                                                                                                      | Stage 1 Full Analysis Set: Empty SPIROMAX       |
| Subject analysis set type                                                                                                                                                                                                                                       | Full analysis                                   |
| Subject analysis set description:<br>All randomized subjects who completed both assessments (so permitting a paired analysis of results).                                                                                                                       |                                                 |
| Subject analysis set title                                                                                                                                                                                                                                      | Stage 1 Full Analysis Set: Empty TURBOHALER     |
| Subject analysis set type                                                                                                                                                                                                                                       | Full analysis                                   |
| Subject analysis set description:<br>All randomized subjects who completed both assessments (so permitting a paired analysis of results).                                                                                                                       |                                                 |
| Subject analysis set title                                                                                                                                                                                                                                      | Stage 2 Full Analysis Set: BF SPIROMAX          |
| Subject analysis set type                                                                                                                                                                                                                                       | Full analysis                                   |
| Subject analysis set description:<br>All randomized subjects who return for assessment of maintenance of inhaler technique at Week 12 using the inhaler (treatment) to which they were randomly assigned (BF SPIROMAX).                                         |                                                 |
| Subject analysis set title                                                                                                                                                                                                                                      | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Subject analysis set type                                                                                                                                                                                                                                       | Full analysis                                   |
| Subject analysis set description:<br>All randomized subjects who return for assessment of maintenance of inhaler technique at Week 12 using the inhaler (treatment) to which they were randomly assigned (SYMBICORT TURBOHALER).                                |                                                 |
| Subject analysis set title                                                                                                                                                                                                                                      | Stage 2 Intent-to-treat: BF SPIROMAX            |
| Subject analysis set type                                                                                                                                                                                                                                       | Intention-to-treat                              |
| Subject analysis set description:<br>All randomized subjects taking BF SPIROMAX                                                                                                                                                                                 |                                                 |
| Subject analysis set title                                                                                                                                                                                                                                      | Stage 2 Intent-to-treat: SYMBICORT TURBOHALER   |
| Subject analysis set type                                                                                                                                                                                                                                       | Intention-to-treat                              |
| Subject analysis set description:<br>All randomized subjects taking SYMBICORT TURBOHALER.                                                                                                                                                                       |                                                 |

### Primary: Stage 1: Number of Subjects Achieving Device Mastery

|                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                       | Stage 1: Number of Subjects Achieving Device Mastery <sup>[1]</sup> |
| End point description:<br>Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an |                                                                     |

assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| 1 day                |         |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Analysis offered as a PDF attachment.

|                             |                                           |                                             |  |  |
|-----------------------------|-------------------------------------------|---------------------------------------------|--|--|
| <b>End point values</b>     | Stage 1 Full Analysis Set: Empty SPIROMAX | Stage 1 Full Analysis Set: Empty TURBOHALER |  |  |
| Subject group type          | Subject analysis set                      | Subject analysis set                        |  |  |
| Number of subjects analysed | 481                                       | 481                                         |  |  |
| Units: subjects             |                                           |                                             |  |  |
| Yes                         | 454                                       | 418                                         |  |  |
| No                          | 27                                        | 63                                          |  |  |

|                                   |                                                               |
|-----------------------------------|---------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Statistical Analysis_Primary Endpoint Stage 1 Device Mastery. |
|-----------------------------------|---------------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Primary: Stage 2: Number of Subjects Maintaining Device Mastery

|                                                                                                             |                                                        |
|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| End point title                                                                                             | Stage 2: Number of Subjects Maintaining Device Mastery |
| End point description:                                                                                      |                                                        |
| Maintenance of device mastery was defined as absence of nurse-observed errors after 12 weeks of device use. |                                                        |
| End point type                                                                                              | Primary                                                |
| End point timeframe:                                                                                        |                                                        |
| 12 weeks                                                                                                    |                                                        |

|                             |                                        |                                                 |  |  |
|-----------------------------|----------------------------------------|-------------------------------------------------|--|--|
| <b>End point values</b>     | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
| Subject group type          | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed | 151                                    | 154                                             |  |  |
| Units: subjects             |                                        |                                                 |  |  |
| Yes                         | 89                                     | 82                                              |  |  |
| No                          | 62                                     | 72                                              |  |  |

### Statistical analyses

|                                         |                                                                                          |
|-----------------------------------------|------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1                                                                   |
| Comparison groups                       | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis | 305                                                                                      |
| Analysis specification                  | Pre-specified                                                                            |
| Analysis type                           | superiority <sup>[2]</sup>                                                               |
| P-value                                 | = 0.316 <sup>[3]</sup>                                                                   |
| Method                                  | Chi-squared                                                                              |
| Parameter estimate                      | Odds ratio (OR)                                                                          |
| Point estimate                          | 1.26                                                                                     |
| Confidence interval                     |                                                                                          |
| level                                   | 95 %                                                                                     |
| sides                                   | 2-sided                                                                                  |
| lower limit                             | 0.8                                                                                      |
| upper limit                             | 1.98                                                                                     |

Notes:

[2] - BF SPIROMAX relative to SYMBICORT TURBOHALER (SYMBICORT TURBOHALER=1.00).

[3] - The p-value for the treatment comparison is based on chi-square; p<0.05 considered statistically significant.

### Secondary: Stage 1: Number of Subjects Achieving Device Mastery by Step 1

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Stage 1: Number of Subjects Achieving Device Mastery by Step 1 |
|-----------------|----------------------------------------------------------------|

End point description:

The number of subjects achieving device mastery by Step 1 (no training/intuitive use) of the device training process. Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 day

| <b>End point values</b>     | Stage 1 Full Analysis Set: Empty SPIROMAX | Stage 1 Full Analysis Set: Empty TURBOHALER |  |  |
|-----------------------------|-------------------------------------------|---------------------------------------------|--|--|
| Subject group type          | Subject analysis set                      | Subject analysis set                        |  |  |
| Number of subjects analysed | 481                                       | 481                                         |  |  |
| Units: subjects             |                                           |                                             |  |  |
| Yes                         | 160                                       | 55                                          |  |  |
| No                          | 321                                       | 426                                         |  |  |

|                                   |                                                           |
|-----------------------------------|-----------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Statistical Analysis_Secondary Endpoint Device Mastery by |
|-----------------------------------|-----------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Stage 1: Number of Subjects Achieving Device Mastery by Step 2

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Stage 1: Number of Subjects Achieving Device Mastery by Step 2 |
|-----------------|----------------------------------------------------------------|

End point description:

The number of subjects achieving device mastery by Step 2 (patient information leaflet) of the device training process. Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 day

| End point values            | Stage 1 Full Analysis Set: Empty SPIROMAX | Stage 1 Full Analysis Set: Empty TURBOHALER |  |  |
|-----------------------------|-------------------------------------------|---------------------------------------------|--|--|
| Subject group type          | Subject analysis set                      | Subject analysis set                        |  |  |
| Number of subjects analysed | 481                                       | 481                                         |  |  |
| Units: subjects             |                                           |                                             |  |  |
| Yes                         | 386                                       | 308                                         |  |  |
| No                          | 95                                        | 173                                         |  |  |

|                            |                                                           |
|----------------------------|-----------------------------------------------------------|
| Attachments (see zip file) | Statistical Analysis_Secundary Endpoint Device Mastery by |
|----------------------------|-----------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Stage 1: Number of Steps Required to Achieve Device Mastery

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Stage 1: Number of Steps Required to Achieve Device Mastery |
|-----------------|-------------------------------------------------------------|

End point description:

Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 day

| End point values              | Stage 1 Full Analysis Set: Empty SPIROMAX | Stage 1 Full Analysis Set: Empty TURBOHALER |  |  |
|-------------------------------|-------------------------------------------|---------------------------------------------|--|--|
| Subject group type            | Subject analysis set                      | Subject analysis set                        |  |  |
| Number of subjects analysed   | 481                                       | 481                                         |  |  |
| Units: training steps         |                                           |                                             |  |  |
| median (full range (min-max)) | 1 (0 to 12)                               | 2 (0 to 15)                                 |  |  |

|                                   |                                                         |
|-----------------------------------|---------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Statistical Analysis_Secundary Endpoint Number of Steps |
|-----------------------------------|---------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Stage 1: Number of Health Care Professional-Observed Errors

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Stage 1: Number of Health Care Professional-Observed Errors |
| End point description:<br>Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. The 6 training steps were as follows: Step 1, intuitive use; Step 2, patient device information leaflet; Step 3, instructional video; Step 4, nurse tuition; Step 5, nurse tuition (1st repeat); Step 6, nurse tuition (2nd repeat). After each training step an assessment of device use was carried out by the nurse using a pre-defined list of inhaler errors. |                                                             |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Secondary                                                   |
| End point timeframe:<br>1 day                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                             |

| End point values                     | Stage 1 Full Analysis Set: Empty SPIROMAX | Stage 1 Full Analysis Set: Empty TURBOHALER |  |  |
|--------------------------------------|-------------------------------------------|---------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                      | Subject analysis set                        |  |  |
| Number of subjects analysed          | 481                                       | 481                                         |  |  |
| Units: errors                        |                                           |                                             |  |  |
| arithmetic mean (standard deviation) | 1.91 ( $\pm$ 0.89)                        | 2.36 ( $\pm$ 0.92)                          |  |  |

|                                   |                                                        |
|-----------------------------------|--------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Statistical Analysis_Secundary Endpoint Number of HCP- |
|-----------------------------------|--------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Stage 1: Subject Preference for the Device

|                                                                                                                              |                                            |
|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| End point title                                                                                                              | Stage 1: Subject Preference for the Device |
| End point description:<br>Total Patient Satisfaction and Preference Questionnaire (PASAPQ) score. The PASAPQ is a multi-item |                                            |

measure of respiratory inhalation device satisfaction and preference designed to be easy to understand and administer to asthma and COPD patients (Kozma et al 2005). The PASAPQ is a two-part questionnaire. Part I consists of 14 questions, the first 13 generating the Performance, Convenience and Total Score domains, and a standalone question for Overall Satisfaction. Part II consists of standalone questions concerning a subject's device preference and willingness to continue use.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 1 day                |           |

| End point values              | Stage 1 Full Analysis Set: Empty SPIROMAX | Stage 1 Full Analysis Set: Empty TURBOHALER |  |  |
|-------------------------------|-------------------------------------------|---------------------------------------------|--|--|
| Subject group type            | Subject analysis set                      | Subject analysis set                        |  |  |
| Number of subjects analysed   | 477 <sup>[4]</sup>                        | 477 <sup>[5]</sup>                          |  |  |
| Units: units on a scale       |                                           |                                             |  |  |
| median (full range (min-max)) | 89.8 (18.37 to 100)                       | 85.71 (14.29 to 100)                        |  |  |

Notes:

[4] - subjects with an assessment

[5] - subjects with an assessment

|                                   |                                                                |
|-----------------------------------|----------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Statistical Analysis_Secondary Endpoint Subject Preference for |
|-----------------------------------|----------------------------------------------------------------|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Stage 2: Total Number of Observed Errors

|                                                                                                                                 |                                          |
|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| End point title                                                                                                                 | Stage 2: Total Number of Observed Errors |
| End point description:                                                                                                          |                                          |
| The total number of observed errors (as observed by health care providers and technology [Vitalograph™ pneumotrac spirometer]). |                                          |
| End point type                                                                                                                  | Secondary                                |
| End point timeframe:                                                                                                            |                                          |
| 12 weeks                                                                                                                        |                                          |

| End point values                     | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|--------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed          | 151                                    | 154                                             |  |  |
| Units: observed errors               |                                        |                                                 |  |  |
| arithmetic mean (standard deviation) | 0.5 (± 0.68)                           | 0.82 (± 1.1)                                    |  |  |

## Statistical analyses

|                                         |                                                                                          |
|-----------------------------------------|------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1                                                                   |
| Comparison groups                       | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis | 305                                                                                      |
| Analysis specification                  | Pre-specified                                                                            |
| Analysis type                           | superiority <sup>[6]</sup>                                                               |
| Parameter estimate                      | rate ratio                                                                               |
| Point estimate                          | 0.62                                                                                     |
| Confidence interval                     |                                                                                          |
| level                                   | 95 %                                                                                     |
| sides                                   | 2-sided                                                                                  |
| lower limit                             | 0.45                                                                                     |
| upper limit                             | 0.84                                                                                     |

Notes:

[6] - BF SPIROMAX relative to SYMBICORT TURBOHALER (SYMBICORT TURBOHALER=1.00). Negative binomial regression was used.

## Secondary: Stage 2: Total Number of Technology-Observed Errors

|                        |                                                                                         |
|------------------------|-----------------------------------------------------------------------------------------|
| End point title        | Stage 2: Total Number of Technology-Observed Errors                                     |
| End point description: | The total number of technology-observed errors (by Vitalograph™ pneumotrac spirometer). |
| End point type         | Secondary                                                                               |
| End point timeframe:   | 12 weeks                                                                                |

| End point values                     | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|--------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed          | 151                                    | 154                                             |  |  |
| Units: errors                        |                                        |                                                 |  |  |
| arithmetic mean (standard deviation) | 0.01 (± 0.08)                          | 0.01 (± 0.08)                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Stage 2: Total Number of Handling Errors

|                        |                                                                                      |
|------------------------|--------------------------------------------------------------------------------------|
| End point title        | Stage 2: Total Number of Handling Errors                                             |
| End point description: | The total number of observed handling errors (as observed by health care providers). |
| End point type         | Secondary                                                                            |
| End point timeframe:   | 12 weeks                                                                             |

| <b>End point values</b>              | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|--------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed          | 151                                    | 154                                             |  |  |
| Units: errors                        |                                        |                                                 |  |  |
| arithmetic mean (standard deviation) | 0.5 (± 0.67)                           | 0.81 (± 1.1)                                    |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Statistical Analysis 1                                                                   |
|-----------------------------------------|------------------------------------------------------------------------------------------|
| Comparison groups                       | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis | 305                                                                                      |
| Analysis specification                  | Pre-specified                                                                            |
| Analysis type                           | superiority <sup>[7]</sup>                                                               |
| Parameter estimate                      | rate ratio                                                                               |
| Point estimate                          | 0.61                                                                                     |
| Confidence interval                     |                                                                                          |
| level                                   | 95 %                                                                                     |
| sides                                   | 2-sided                                                                                  |
| lower limit                             | 0.44                                                                                     |
| upper limit                             | 0.84                                                                                     |

Notes:

[7] - Negative binomial regression model was used.

## Secondary: Stage 2: Difference in Handling Errors from Stage 1 to Stage 2 (12 weeks)

|                        |                                                                                                                                                                                 |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Stage 2: Difference in Handling Errors from Stage 1 to Stage 2 (12 weeks)                                                                                                       |
| End point description: | The difference in number of handling errors identified following training using patient device information leaflet at Stage 1 and after 12 weeks of treatment (end of Stage 2). |
| End point type         | Secondary                                                                                                                                                                       |
| End point timeframe:   | 12 weeks                                                                                                                                                                        |

| End point values                     | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|--------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed          | 151                                    | 154                                             |  |  |
| Units: errors                        |                                        |                                                 |  |  |
| arithmetic mean (standard deviation) | -0.95 (± 1.72)                         | -2.01 (± 2.52)                                  |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical Analysis 1                                                                   |
|-----------------------------------------|------------------------------------------------------------------------------------------|
| Comparison groups                       | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis | 305                                                                                      |
| Analysis specification                  | Pre-specified                                                                            |
| Analysis type                           | superiority <sup>[8]</sup>                                                               |
| Parameter estimate                      | rate ratio                                                                               |
| Point estimate                          | 1.05                                                                                     |
| Confidence interval                     |                                                                                          |
| level                                   | 95 %                                                                                     |
| sides                                   | 2-sided                                                                                  |
| lower limit                             | 0.57                                                                                     |
| upper limit                             | 1.54                                                                                     |

Notes:

[8] - Negative binomial regression model was used.

## Secondary: Stage 2: Treatment Adherence

|                        |                                                                                   |
|------------------------|-----------------------------------------------------------------------------------|
| End point title        | Stage 2: Treatment Adherence                                                      |
| End point description: | Percentage of treatment adherence by subject as assessed by device dose counters. |
| End point type         | Secondary                                                                         |
| End point timeframe:   | 12 weeks                                                                          |

| End point values            | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|-----------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type          | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed | 151                                    | 154                                             |  |  |
| Units: subjects             |                                        |                                                 |  |  |
| </= 50% adherence           | 60                                     | 61                                              |  |  |
| 51% to 70% adherence        | 19                                     | 16                                              |  |  |
| 71% to 99% adherence        | 70                                     | 71                                              |  |  |
| 100% adherence              | 2                                      | 6                                               |  |  |

## Statistical analyses

|                                         |                                                                                          |
|-----------------------------------------|------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1                                                                   |
| Comparison groups                       | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis | 305                                                                                      |
| Analysis specification                  | Pre-specified                                                                            |
| Analysis type                           | superiority                                                                              |
| P-value                                 | = 0.523 <sup>[9]</sup>                                                                   |
| Method                                  | Chi-squared                                                                              |

Notes:

[9] -  $p < 0.05$  is considered statistically significant.

## Secondary: Stage 2: Change in 6-item Asthma Control Questionnaire (ACQ) From Baseline to 4, 8, and 12 Weeks

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Stage 2: Change in 6-item Asthma Control Questionnaire (ACQ) From Baseline to 4, 8, and 12 Weeks |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

Change in the 6-item ACQ from Baseline to 4, 8, and 12 weeks. The ACQ is a 7-item, validated tool for assessing asthma control (Juniper et al 1999). Thinking about their asthma for the last 7 days, subjects were asked to evaluate their asthma against 5 symptom items and a rescue bronchodilator use question using a 7-point scale (0=no impairment and 6=maximum impairment). Spirometry data were used to grade the percent predicted forced expiratory volume in 1 second (FEV1) on a 7-point scale (0 to 6). The score is the mean of the first 6 questions (excluding the FEV1 question), generating a value from 0 (totally controlled) to 6 (severely uncontrolled). A negative change from Baseline indicates improvement.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 4, 8, and 12 weeks

| <b>End point values</b>              | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|--------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed          | 151 <sup>[10]</sup>                    | 154 <sup>[11]</sup>                             |  |  |
| Units: units on a scale              |                                        |                                                 |  |  |
| arithmetic mean (standard deviation) |                                        |                                                 |  |  |
| Week 4; n=142, 140                   | -0.22 (± 0.83)                         | -0.33 (± 0.81)                                  |  |  |
| Week 8; n=140, 143                   | -0.2 (± 0.98)                          | -0.3 (± 1.04)                                   |  |  |
| Week 12; n=137, 147                  | -0.22 (± 0.95)                         | -0.36 (± 1.05)                                  |  |  |

Notes:

[10] - n=number of subjects with an assessment at Baseline and given time point

[11] - n=number of subjects with an assessment at Baseline and given time point

## Statistical analyses

| Statistical analysis title                  | Statistical Analysis 1                                                                   |
|---------------------------------------------|------------------------------------------------------------------------------------------|
| Statistical analysis description:<br>Week 4 |                                                                                          |
| Comparison groups                           | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis     | 305                                                                                      |
| Analysis specification                      | Pre-specified                                                                            |
| Analysis type                               | superiority                                                                              |
| Parameter estimate                          | treatment difference                                                                     |
| Point estimate                              | 0.11                                                                                     |
| Confidence interval                         |                                                                                          |
| level                                       | 95 %                                                                                     |
| sides                                       | 2-sided                                                                                  |
| lower limit                                 | -0.08                                                                                    |
| upper limit                                 | 0.3                                                                                      |

| Statistical analysis title                  | Statistical Analysis 2                                                                   |
|---------------------------------------------|------------------------------------------------------------------------------------------|
| Statistical analysis description:<br>Week 8 |                                                                                          |
| Comparison groups                           | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis     | 305                                                                                      |
| Analysis specification                      | Pre-specified                                                                            |
| Analysis type                               | superiority                                                                              |
| Parameter estimate                          | treatment difference                                                                     |
| Point estimate                              | 0.1                                                                                      |
| Confidence interval                         |                                                                                          |
| level                                       | 95 %                                                                                     |
| sides                                       | 2-sided                                                                                  |
| lower limit                                 | -0.14                                                                                    |
| upper limit                                 | 0.33                                                                                     |

| Statistical analysis title                   | Statistical Analysis 3                                                                   |
|----------------------------------------------|------------------------------------------------------------------------------------------|
| Statistical analysis description:<br>Week 12 |                                                                                          |
| Comparison groups                            | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis      | 305                                                                                      |
| Analysis specification                       | Pre-specified                                                                            |
| Analysis type                                | superiority                                                                              |
| Parameter estimate                           | treatment difference                                                                     |
| Point estimate                               | 0.13                                                                                     |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.1    |
| upper limit         | 0.37    |

## Secondary: Stage 2: Change in the 7-item ACQ From Baseline to Week 12

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Stage 2: Change in the 7-item ACQ From Baseline to Week 12 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                            |
| Change in 7-item ACQ (including FEV1 question) from baseline to Week 12. The ACQ is a 7-item, validated tool for assessing asthma control (Juniper et al 1999). Thinking about their asthma for the last 7 days, subjects were asked to evaluate their asthma against 5 symptom items and a rescue bronchodilator use question using a 7-point scale (0=no impairment and 6=maximum impairment). Spirometry data were used to grade the percent predicted FEV1 on a 7-point scale (0 to 6). The ACQ score is the mean of the 7 questions, generating a value from 0 (totally controlled) to 6 (severely uncontrolled). A negative change from Baseline indicates improvement. |                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Secondary                                                  |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                            |
| Baseline, Week 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                            |

| End point values                     | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|--------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed          | 145 <sup>[12]</sup>                    | 149 <sup>[13]</sup>                             |  |  |
| Units: units on a scale              |                                        |                                                 |  |  |
| arithmetic mean (standard deviation) | -0.2 (± 0.78)                          | -0.31 (± 0.92)                                  |  |  |

Notes:

[12] - subjects with an assessment at Baseline and Week 12

[13] - subjects with an assessment at Baseline and Week 12

## Statistical analyses

|                                         |                                                                                          |
|-----------------------------------------|------------------------------------------------------------------------------------------|
| Statistical analysis title              | Statistical Analysis 1                                                                   |
| Comparison groups                       | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis | 294                                                                                      |
| Analysis specification                  | Pre-specified                                                                            |
| Analysis type                           | superiority                                                                              |
| Parameter estimate                      | treatment difference                                                                     |
| Point estimate                          | 0.11                                                                                     |
| Confidence interval                     |                                                                                          |
| level                                   | 95 %                                                                                     |
| sides                                   | 2-sided                                                                                  |
| lower limit                             | -0.09                                                                                    |
| upper limit                             | 0.3                                                                                      |

---

**Secondary: Stage 2: Time to First Treatment Failure**

---

|                 |                                          |
|-----------------|------------------------------------------|
| End point title | Stage 2: Time to First Treatment Failure |
|-----------------|------------------------------------------|

End point description:

The time to treatment failure, defined as change of asthma treatment or treatment for an asthma exacerbation or lower respiratory tract infection.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

---

| End point values                     | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|--------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed          | 151 <sup>[14]</sup>                    | 154 <sup>[15]</sup>                             |  |  |
| Units: days                          |                                        |                                                 |  |  |
| arithmetic mean (standard deviation) | 76.38 (± 21.42)                        | 73.95 (± 24.27)                                 |  |  |

Notes:

[14] - subjects with treatment failure=29

[15] - subjects with treatment failure=40

**Statistical analyses**

| Statistical analysis title              | Statistical Analysis 1                                                                   |
|-----------------------------------------|------------------------------------------------------------------------------------------|
| Comparison groups                       | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |
| Number of subjects included in analysis | 305                                                                                      |
| Analysis specification                  | Pre-specified                                                                            |
| Analysis type                           | superiority                                                                              |
| P-value                                 | = 0.159 <sup>[16]</sup>                                                                  |
| Method                                  | Log-rank (Mantel-Cox)                                                                    |

Notes:

[16] - p < 0.05 is considered statistically significant.

---

**Secondary: Stage 2: Number of Severe Asthma Exacerbations**

---

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Stage 2: Number of Severe Asthma Exacerbations |
|-----------------|------------------------------------------------|

End point description:

Number of severe asthma exacerbations, defined as a hospitalization or emergency room attendance for asthma, or an acute course of oral corticosteroids.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

---

| End point values            | Stage 2 Intent-to-treat: BF SPIROMAX | Stage 2 Intent-to-treat: SYMBICORT TURBOHALER |  |  |
|-----------------------------|--------------------------------------|-----------------------------------------------|--|--|
| Subject group type          | Subject analysis set                 | Subject analysis set                          |  |  |
| Number of subjects analysed | 197                                  | 197                                           |  |  |
| Units: subjects             |                                      |                                               |  |  |
| No exacerbations            | 178                                  | 176                                           |  |  |
| One exacerbation            | 18                                   | 20                                            |  |  |
| Two exacerbations           | 1                                    | 1                                             |  |  |
| Three or more exacerbations | 0                                    | 0                                             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Stage 2: Impact of Maintaining Device Mastery on Time to Treatment Failure

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Stage 2: Impact of Maintaining Device Mastery on Time to Treatment Failure |
| End point description:<br>The impact of maintaining device mastery on time to treatment failure (defined as change of asthma treatment or treatment for an asthma exacerbation or lower respiratory tract infection) was assessed by comparing the time to treatment failure for subjects with and without device mastery. Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. |                                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secondary                                                                  |
| End point timeframe:<br>Week 12                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                            |

| End point values                     | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|--------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed          | 151 <sup>[17]</sup>                    | 154 <sup>[18]</sup>                             |  |  |
| Units: days                          |                                        |                                                 |  |  |
| arithmetic mean (standard deviation) |                                        |                                                 |  |  |
| Device mastery=yes; n=89, 82         | 72.99 (± 22.38)                        | 75.93 (± 22.59)                                 |  |  |
| Device mastery=no; n=62, 72          | 81.24 (± 19.11)                        | 71.69 (± 26.03)                                 |  |  |

Notes:

[17] - n=subjects with or without device mastery

[18] - n=subjects with or without device mastery

## Statistical analyses

|                            |                                                                                          |
|----------------------------|------------------------------------------------------------------------------------------|
| Statistical analysis title | Statistical Analysis 1                                                                   |
| Comparison groups          | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 305                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[19]</sup> |
| Parameter estimate                      | Hazard ratio (HR)           |
| Point estimate                          | 1.06                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.82                        |
| upper limit                             | 1.38                        |

Notes:

[19] - Cox Regression with device and device mastery as covariates.

## Secondary: Stage 2: Impact of Maintaining Device Mastery on Asthma Control

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | Stage 2: Impact of Maintaining Device Mastery on Asthma Control |
|-----------------|-----------------------------------------------------------------|

End point description:

The impact of maintaining device mastery on asthma control was assessed by comparing the 7-item ACQ scores for subjects with and without device mastery. The ACQ is a 7-item, validated tool for assessing asthma control (Juniper et al 1999). Thinking about their asthma for the last 7 days, subjects were asked to evaluate their asthma against 5 symptom items and a rescue bronchodilator use question using a 7-point scale (0=no impairment and 6=maximum impairment). Spirometry data were used to grade the percent predicted FEV1 on a 7-point scale (0 to 6). The ACQ score is the mean of the 7 questions, generating a value from 0 (totally controlled) to 6 (severely uncontrolled). Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

| End point values                     | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|--------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed          | 151 <sup>[20]</sup>                    | 154 <sup>[21]</sup>                             |  |  |
| Units: units on a scale              |                                        |                                                 |  |  |
| arithmetic mean (standard deviation) |                                        |                                                 |  |  |
| Device mastery=yes; n=85, 79         | 1.25 (± 1.05)                          | 1.35 (± 0.95)                                   |  |  |
| Device mastery=no; n=60, 70          | 1.46 (± 0.97)                          | 1.37 (± 0.97)                                   |  |  |

Notes:

[20] - n=subjects with or without device mastery

[21] - n=subjects with or without device mastery

## Statistical analyses

|                            |                                                                                          |
|----------------------------|------------------------------------------------------------------------------------------|
| Statistical analysis title | Statistical Analysis 1                                                                   |
| Comparison groups          | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 305               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 2.54              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | -1.64             |
| upper limit                             | 7.71              |

## Secondary: Stage 2: Percentage of Patients Maintaining Device Mastery Relating to Dose Preparation Errors

|                                                                                                                                                                                                                                                                                                                                               |                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                               | Stage 2: Percentage of Patients Maintaining Device Mastery Relating to Dose Preparation Errors |
| End point description:                                                                                                                                                                                                                                                                                                                        |                                                                                                |
| Device mastery was defined as the absence of nurse-observed errors by the end of Step 3 of a 6-step standardized device training protocol for each device. This analysis is limited to errors affecting dose preparation, such as not twisting the base as far as possible, until it clicks and not turning it back to its original position. |                                                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                | Secondary                                                                                      |
| End point timeframe:                                                                                                                                                                                                                                                                                                                          |                                                                                                |
| 12 weeks                                                                                                                                                                                                                                                                                                                                      |                                                                                                |

| End point values                    | Stage 2 Full Analysis Set: BF SPIROMAX | Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |  |  |
|-------------------------------------|----------------------------------------|-------------------------------------------------|--|--|
| Subject group type                  | Subject analysis set                   | Subject analysis set                            |  |  |
| Number of subjects analysed         | 151                                    | 154                                             |  |  |
| Units: percentage of participants   |                                        |                                                 |  |  |
| number (not applicable)             |                                        |                                                 |  |  |
| Yes: maintained device mastery      | 76.2                                   | 69.5                                            |  |  |
| No: did not maintain device mastery | 23.8                                   | 30.5                                            |  |  |

## Statistical analyses

|                            |                                                                                          |
|----------------------------|------------------------------------------------------------------------------------------|
| Statistical analysis title | Mastery: Dose Prep Errors Only                                                           |
| Comparison groups          | Stage 2 Full Analysis Set: BF SPIROMAX v Stage 2 Full Analysis Set: SYMBICORT TURBOHALER |

|                                         |                 |
|-----------------------------------------|-----------------|
| Number of subjects included in analysis | 305             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority     |
| P-value                                 | = 0.19          |
| Method                                  | Chi-squared     |
| Parameter estimate                      | Odds ratio (OR) |
| Point estimate                          | 1.4             |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.84            |
| upper limit                             | 2.34            |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Through Week 12

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

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

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | BF SPIROMAX |
|-----------------------|-------------|

Reporting group description:

Inhaled corticosteroid/long-acting  $\beta$ 2-agonist via the BF SPIROMAX device for 12 weeks of therapy.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | SYMBICORT TURBOHALER |
|-----------------------|----------------------|

Reporting group description:

Inhaled corticosteroid/long-acting  $\beta$ 2-agonist via the SYMBICORT TURBOHALER device for 12 weeks of therapy.

| Serious adverse events                            | BF SPIROMAX     | SYMBICORT TURBOHALER |  |
|---------------------------------------------------|-----------------|----------------------|--|
| Total subjects affected by serious adverse events |                 |                      |  |
| subjects affected / exposed                       | 4 / 197 (2.03%) | 8 / 197 (4.06%)      |  |
| number of deaths (all causes)                     | 0               | 0                    |  |
| number of deaths resulting from adverse events    |                 |                      |  |
| Injury, poisoning and procedural complications    |                 |                      |  |
| Thermal burn                                      |                 |                      |  |
| subjects affected / exposed                       | 0 / 197 (0.00%) | 1 / 197 (0.51%)      |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1                |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0                |  |
| Vascular disorders                                |                 |                      |  |
| Hypotension                                       |                 |                      |  |
| subjects affected / exposed                       | 0 / 197 (0.00%) | 1 / 197 (0.51%)      |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1                |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0                |  |
| Cardiac disorders                                 |                 |                      |  |
| Angina pectoris                                   |                 |                      |  |
| subjects affected / exposed                       | 1 / 197 (0.51%) | 0 / 197 (0.00%)      |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0                |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0                |  |
| Atrial flutter                                    |                 |                      |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 197 (0.00%) | 1 / 197 (0.51%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Atrioventricular block                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) | 1 / 197 (0.51%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest pain                                           |                 |                 |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) | 2 / 197 (1.02%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders             |                 |                 |  |
| Ovarian mass                                         |                 |                 |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) | 1 / 197 (0.51%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Asthma                                               |                 |                 |  |
| subjects affected / exposed                          | 2 / 197 (1.02%) | 1 / 197 (0.51%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                         |                 |                 |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) | 1 / 197 (0.51%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                          |                 |                 |  |
| Renal failure acute                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) | 1 / 197 (0.51%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Infections and infestations                          |                 |                 |  |
| Lower respiratory tract infection                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 197 (0.51%) | 1 / 197 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 197 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | BF SPIROMAX       | SYMBICORT TURBOHALER |  |
|-------------------------------------------------------|-------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                   |                      |  |
| subjects affected / exposed                           | 28 / 197 (14.21%) | 39 / 197 (19.80%)    |  |
| Respiratory, thoracic and mediastinal disorders       |                   |                      |  |
| Cough                                                 |                   |                      |  |
| subjects affected / exposed                           | 11 / 197 (5.58%)  | 12 / 197 (6.09%)     |  |
| occurrences (all)                                     | 11                | 12                   |  |
| Infections and infestations                           |                   |                      |  |
| Lower respiratory tract infection                     |                   |                      |  |
| subjects affected / exposed                           | 16 / 197 (8.12%)  | 29 / 197 (14.72%)    |  |
| occurrences (all)                                     | 16                | 29                   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 28 January 2014 | The following major procedural changes (not all-inclusive) were made to the protocol: <ul style="list-style-type: none"><li>• removal of allowance for subject rescreening</li><li>• changing the ACQ and PASAPQ from verbally administered to written completion by the subject</li></ul>                                                    |
| 24 March 2014   | The following major procedural changes (not all-inclusive) were made to the protocol: <ul style="list-style-type: none"><li>• amended the errata associated with BF SPIROMAX devices resulting from recently available stability data</li><li>• removed the collection of peripheral blood for eosinophil assessment as a procedure</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported