



Clinical trial results:

A 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of acclidinium bromide 400 g/formoterol fumarate 12 g fixed-dose combination BID compared with each monotherapy (acclidinium bromide 400 g BID and formoterol fumarate 12 g BID) and tiotropium 18 g QD when administered to subjects with stable chronic obstructive pulmonary disease

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2015-005444-33 |
| Trial protocol | GB HU CZ BG ES PL |
| Global end of trial date | 08 June 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 June 2018 |
| First version publication date | 06 June 2018 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D6571C00001 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02796677 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | AstraZeneca AB |
| Sponsor organisation address | Södertälje, Södertälje, Sweden, 151 85 |
| Public contact | Information Centre, AstraZeneca AB, Information Centre, AstraZeneca AB, +1 800 2369933, information.centre@astrazeneca.com |
| Scientific contact | Global Clinical Leader, AstraZeneca AB, +46 766 346712, clinicaltrialtransparency@astrazeneca.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 June 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 June 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 June 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

For United States (US): To assess the bronchodilatory effect of Acclidinium bromide/Formoterol fumarate (AB/FF) 400/12 µg compared to each individual component when administered twice daily (BID) via inhalation to chronic obstructive pulmonary disease (COPD) subjects. For Market Access: To assess the non-inferior bronchodilation of AB 400 µg BID as compared to Tiotropium (TIO) 18 µg once daily (QD) in COPD subjects.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation /Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics. Each subject was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Each subject was notified that they were free to discontinue from the study at any time and were given the opportunity to ask questions and allowed time to consider the information provided. Each subject provided signed and dated ICF before conducting any procedure specifically for the study. A copy of the signed informed consent form (ICF) was given to the subject. Any incentives for subjects who participated in the study as well as any provisions for subjects harmed as a consequence of study participation were described in the ICF that was approved by an Ethics Committee.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 05 July 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 699 |
| Country: Number of subjects enrolled | Germany: 349 |
| Country: Number of subjects enrolled | Poland: 124 |
| Country: Number of subjects enrolled | Hungary: 116 |
| Country: Number of subjects enrolled | Bulgaria: 106 |
| Country: Number of subjects enrolled | Ukraine: 110 |
| Country: Number of subjects enrolled | United Kingdom: 34 |
| Country: Number of subjects enrolled | Czech Republic: 32 |
| Country: Number of subjects enrolled | Spain: 7 |

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Israel: 17 |
| Worldwide total number of subjects | 1594 |
| EEA total number of subjects | 768 |

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) | 795 |
| From 65 to 84 years | 793 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details:

Study was conducted on subjects with stable COPD, in 11 countries: United States (US), Germany, Poland, Hungary, Bulgaria, Ukraine, United Kingdom (UK), Czech Republic, Spain, Israel & Russia (was not finally started).

Pre-assignment

Screening details:

Eligible subjects signed ICF; entered screening period (Run-in; 14 ± 3 days), inclusion/exclusion criteria were checked by medical & COPD history, physical examination, blood pressure, electrocardiogram, laboratory tests, concomitant drugs & COPD Assessment Test [CAT] & post-bronchodilator forced expiratory volume in 1 second [FEV1]

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Period 1: Overall Study |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | No |
| Arm title | Acclidinium bromide (AB)/Formoterol fumarate (FF) 400/12 µg |

Arm description:

Randomized subjects received AB 400 µg/FF 12 µg oral inhalation powder twice daily (BID) via dry powder inhaler (DPI).

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Acclidinium bromide/Formoterol fumarate |
| Investigational medicinal product code | |
| Other name | Pressair®/Genuair® Dry Powder Inhaler |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

AB/FF 400/12 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

| | |
|------------------|-----------|
| Arm title | AB 400 µg |
|------------------|-----------|

Arm description:

Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Acclidinium bromide |
| Investigational medicinal product code | |
| Other name | Pressair®/Genuair® Dry Powder Inhaler |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

AB 400 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

| | |
|------------------|----------|
| Arm title | FF 12 µg |
|------------------|----------|

Arm description:

Randomized subjects received FF 12 µg oral inhalation powder BID via DPI.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Formoterol fumarate |
| Investigational medicinal product code | |
| Other name | Pressair®/Genuair® Dry Powder Inhaler |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

FF 12 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

| | |
|------------------|------------------------|
| Arm title | Tiotropium (TIO) 18 µg |
|------------------|------------------------|

Arm description:

Randomized subjects received TIO 18 µg oral inhalation powder in capsule BID via DPI.

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tiotropium |
| Investigational medicinal product code | |
| Other name | HandiHaler® Dry Powder Inhaler |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

TIO 18 µg inhalation powder QD (morning) via DPI for 24 weeks

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Tiotropium |
| Investigational medicinal product code | |
| Other name | Pressair®/Genuair® Dry Powder Inhaler |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

TIO 18 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

| Number of subjects in period 1 | Aclidinium bromide (AB)/Formoterol fumarate (FF) 400/12 µg | AB 400 µg | FF 12 µg |
|--------------------------------|--|-----------|----------|
| | | | |
| Started | 317 | 478 | 320 |
| Completed | 279 | 405 | 267 |
| Not completed | 38 | 73 | 53 |
| Consent withdrawn by subject | 4 | 14 | 6 |
| Adverse event, non-fatal | 11 | 22 | 14 |
| Lost to follow-up | 1 | 5 | 2 |
| Progressive disease | 6 | 15 | 13 |
| Reason not mentioned | 2 | 3 | - |
| Protocol deviation | 7 | 5 | 4 |
| Lack of efficacy | 7 | 9 | 14 |

| | |
|---------------------------------------|------------------------|
| Number of subjects in period 1 | Tiotropium (TIO) 18 µg |
| Started | 479 |
| Completed | 405 |
| Not completed | 74 |
| Consent withdrawn by subject | 7 |

| | |
|--------------------------|----|
| Adverse event, non-fatal | 14 |
| Lost to follow-up | 2 |
| Progressive disease | 18 |
| Reason not mentioned | 5 |
| Protocol deviation | 8 |
| Lack of efficacy | 20 |

Period 2

| | |
|------------------------------|----------------------------------|
| Period 2 title | Intent-to-treat (ITT) population |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | AB/FF 400/12 µg |

Arm description:

Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder twice daily (BID) via dry powder inhaler (DPI).

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Acclidinium bromide/Formoterol fumarate |
| Investigational medicinal product code | |
| Other name | Pressair®/Genuair® Dry Powder Inhaler |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

AB/FF 400/12 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

| | |
|------------------|-----------|
| Arm title | AB 400 µg |
|------------------|-----------|

Arm description:

Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Acclidinium bromide |
| Investigational medicinal product code | |
| Other name | Pressair®/Genuair® Dry Powder Inhaler |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

AB 400 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

| | |
|------------------|----------|
| Arm title | FF 12 µg |
|------------------|----------|

Arm description:

Randomized subjects received FF 12 µg oral inhalation powder BID via DPI.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Formoterol fumarate |
| Investigational medicinal product code | |
| Other name | Pressair®/Genuair® Dry Powder Inhaler |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

FF 12 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

| | |
|------------------|-----------|
| Arm title | TIO 18 µg |
|------------------|-----------|

Arm description:

Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI.

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tiotropium |
| Investigational medicinal product code | |
| Other name | HandiHaler® Dry Powder Inhaler |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

TIO 18 µg inhalation powder QD (morning) via DPI for 24 weeks

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Subject disposition (Period 1) data were presented for the randomized population (N = 1594). The baseline characteristics and endpoints data were presented for the safety population and Intent-to-treat population (ITT; Period 2), respectively; in these two population sets, the number of subjects (N) was 1583. Hence, period 2 (ITT) was mentioned as the baseline period.

| Number of subjects in period 2^[2] | AB/FF 400/12 µg | AB 400 µg | FF 12 µg |
|---|-----------------|-----------|----------|
| Started | 314 | 475 | 319 |
| Completed | 314 | 475 | 319 |

| Number of subjects in period 2^[2] | TIO 18 µg |
|---|-----------|
| Started | 475 |
| Completed | 475 |

Notes:

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

Justification: All screened subjects were mentioned in the worldwide population of the trial whereas subjects who received at least 1 dose of the investigational product were mentioned in the ITT population (baseline period). Non-eligible subjects were not randomized in the study.

Baseline characteristics

Reporting groups

| | |
|--|-----------------|
| Reporting group title | AB/FF 400/12 µg |
| Reporting group description: | |
| Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder twice daily (BID) via dry powder inhaler (DPI). | |
| Reporting group title | AB 400 µg |
| Reporting group description: | |
| Randomized subjects received AB 400 µg oral inhalation powder BID via DPI. | |
| Reporting group title | FF 12 µg |
| Reporting group description: | |
| Randomized subjects received FF 12 µg oral inhalation powder BID via DPI. | |
| Reporting group title | TIO 18 µg |
| Reporting group description: | |
| Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI. | |

| Reporting group values | AB/FF 400/12 µg | AB 400 µg | FF 12 µg |
|---|-----------------|-----------|----------|
| Number of subjects | 314 | 475 | 319 |
| Age categorical | | | |
| Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 166 | 270 | 168 |
| From 65-84 years | 146 | 205 | 151 |
| 85 years and over | 2 | 0 | 0 |
| Age Continuous | | | |
| Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug. | | | |
| Units: years | | | |
| arithmetic mean | 64.4 | 64.4 | 64.7 |
| standard deviation | ± 8.5 | ± 8.1 | ± 8.3 |
| Sex: Female, Male | | | |
| Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug. | | | |
| Units: Subjects | | | |
| Female | 121 | 171 | 129 |
| Male | 193 | 304 | 190 |

| Reporting group values | TIO 18 µg | Total | |
|---|-----------|-------|--|
| Number of subjects | 475 | 1583 | |
| Age categorical | | | |
| Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |

| | | | |
|---|-------|-----|--|
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 263 | 867 | |
| From 65-84 years | 209 | 711 | |
| 85 years and over | 3 | 5 | |
| Age Continuous | | | |
| Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug. | | | |
| Units: years | | | |
| arithmetic mean | 64.0 | | |
| standard deviation | ± 8.6 | - | |
| Sex: Female, Male | | | |
| Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug. | | | |
| Units: Subjects | | | |
| Female | 199 | 620 | |
| Male | 276 | 963 | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Acclidinium bromide (AB)/Formoterol fumarate (FF) 400/12 µg |
| Reporting group description: Randomized subjects received AB 400 µg/FF 12 µg oral inhalation powder twice daily (BID) via dry powder inhaler (DPI). | |
| Reporting group title | AB 400 µg |
| Reporting group description: Randomized subjects received AB 400 µg oral inhalation powder BID via DPI. | |
| Reporting group title | FF 12 µg |
| Reporting group description: Randomized subjects received FF 12 µg oral inhalation powder BID via DPI. | |
| Reporting group title | Tiotropium (TIO) 18 µg |
| Reporting group description: Randomized subjects received TIO 18 µg oral inhalation powder in capsule BID via DPI. | |
| Reporting group title | AB/FF 400/12 µg |
| Reporting group description: Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder twice daily (BID) via dry powder inhaler (DPI). | |
| Reporting group title | AB 400 µg |
| Reporting group description: Randomized subjects received AB 400 µg oral inhalation powder BID via DPI. | |
| Reporting group title | FF 12 µg |
| Reporting group description: Randomized subjects received FF 12 µg oral inhalation powder BID via DPI. | |
| Reporting group title | TIO 18 µg |
| Reporting group description: Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI. | |
| Subject analysis set title | AB/FF 400/12 µg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder BID via DPI. | |
| Subject analysis set title | AB 400 µg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Randomized subjects received AB 400 µg oral inhalation powder BID via DPI. | |
| Subject analysis set title | AB 400 µg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Randomized subjects received AB 400 µg oral inhalation powder BID via DPI. | |
| Subject analysis set title | FF 12 µg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Randomized subjects received FF 12 µg oral inhalation powder BID via DPI. | |
| Subject analysis set title | TIO 18 µg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI. | |
| Subject analysis set title | TIO 18 µg |
| Subject analysis set type | Intention-to-treat |

Primary: Change from baseline in 1-hour morning post-dose dose forced expiratory volume in 1 second (FEV1) of AB/FF 400/12 µg compared to AB 400 µg at week 24

| | |
|-----------------|---|
| End point title | Change from baseline in 1-hour morning post-dose dose forced expiratory volume in 1 second (FEV1) of AB/FF 400/12 µg compared to AB 400 µg at week 24 |
|-----------------|---|

End point description:

To assess the bronchodilatory effect by evaluating the mean changes from baseline in FEV1 at 1 hour post-dose of AB/FF 400/12 µg compared to AB 400 µg after administration of oral inhalation powder BID via DPI to subjects with COPD. Baseline was defined as the average of the two FEV1 values measured just prior to the administration of the first dose of investigational product (IP) at randomization Visit. If one of the two was missing, then the available one would be used as baseline value.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At baseline 1-hour postdose and Week 24

| End point values | AB/FF 400/12 µg | AB 400 µg | FF 12 µg | TIO 18 µg |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 274 | 398 | 258 | 400 |
| Units: Litres | | | | |
| least squares mean (standard error) | 0.253 (± 0.013) | 0.169 (± 0.011) | 0.168 (± 0.013) | 0.161 (± 0.011) |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | AB/FF 400/12 µg versus AB 400 µg |
|-----------------------------------|----------------------------------|

Statistical analysis description:

Number of subjects analyzed were 274 in AB/FF 400/12 µg arm and 398 in AB 400 µg arm.

| | |
|---|-----------------------------------|
| Comparison groups | AB/FF 400/12 µg v AB 400 µg |
| Number of subjects included in analysis | 672 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | LS mean difference |
| Point estimate | 0.084 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.051 |
| upper limit | 0.117 |

Primary: Change from baseline in morning predose (trough) FEV1 of AB/FF 400/12

µg compared to FF 12 µg at week 24

| | |
|-----------------|--|
| End point title | Change from baseline in morning predose (trough) FEV1 of AB/FF 400/12 µg compared to FF 12 µg at week 24 |
|-----------------|--|

End point description:

To assess the bronchodilatory effect by evaluating the mean changes from baseline in FEV1 in morning pre-dose (trough) of AB/FF 400/12 µg compared to FF 12 µg after administration of oral inhalation powder BID via DPI to subjects with COPD. Morning pre-dose (trough) FEV1 was defined as the average of the corresponding -30 minute and 0 minute before the morning study medication administration at Week 24. If one time-point was missing then the available one would be used as morning pre-dose.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At baseline morning predose and Week 24

| End point values | AB/FF 400/12 µg | AB 400 µg | FF 12 µg | TIO 18 µg |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 274 | 401 | 259 | 401 |
| Units: Litres | | | | |
| least squares mean (standard error) | 0.080 (± 0.014) | 0.066 (± 0.012) | 0.025 (± 0.014) | 0.060 (± 0.012) |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | AB/FF 400/12 µg versus FF 12 µg |
|----------------------------|---------------------------------|

Statistical analysis description:

Number of subjects analyzed were 274 in AB/FF 400/12 µg arm and 259 in AB 400 µg arm.

| | |
|---|-----------------------------------|
| Comparison groups | AB/FF 400/12 µg v FF 12 µg |
| Number of subjects included in analysis | 533 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0009 |
| Method | Mixed model for repeated measures |
| Parameter estimate | LS mean difference |
| Point estimate | 0.055 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.023 |
| upper limit | 0.088 |

Primary: Change from baseline in morning predose (trough) FEV1 at week 24 comparing AB 400 µg versus TIO 18 µg to demonstrate non-inferiority

| | |
|-----------------|--|
| End point title | Change from baseline in morning predose (trough) FEV1 at week 24 comparing AB 400 µg versus TIO 18 µg to demonstrate non-inferiority |
|-----------------|--|

End point description:

To assess the non-inferior bronchodilatory effect by evaluating the mean changes from baseline in FEV1 in morning pre-dose (trough) of AB 400 µg BID compared to TIO 18 µg QD after administration of oral inhalation powder via DPI to subjects with COPD.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At baseline morning predose and Week 24

| End point values | AB 400 µg | TIO 18 µg | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 369 | 369 | | |
| Units: Litres | | | | |
| least squares mean (standard error) | 0.064 (± 0.013) | 0.057 (± 0.013) | | |

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | AB 400 µg versus TIO 18 µg |
|----------------------------|----------------------------|

Statistical analysis description:

Number of subjects analyzed were 369 in AB 400 µg arm and 369 in TIO 18 µg arm.

| | |
|-------------------|-----------------------|
| Comparison groups | AB 400 µg v TIO 18 µg |
|-------------------|-----------------------|

| | |
|---|-----|
| Number of subjects included in analysis | 738 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|--------------------------------|
| Analysis type | non-inferiority ^[1] |
|---------------|--------------------------------|

| | |
|---------|----------|
| P-value | = 0.6377 |
|---------|----------|

| | |
|--------|-----------------------------------|
| Method | Mixed model for repeated measures |
|--------|-----------------------------------|

| | |
|--------------------|--------------------|
| Parameter estimate | LS mean difference |
|--------------------|--------------------|

| | |
|----------------|-------|
| Point estimate | 0.007 |
|----------------|-------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|--------|
| lower limit | -0.021 |
|-------------|--------|

| | |
|-------------|-------|
| upper limit | 0.035 |
|-------------|-------|

Notes:

[1] - Non-inferiority was established by showing that the lower bound of the two-sided 95% confidence interval for change from baseline in morning pre-dose (trough) FEV1 at week 24 when compared AB 400 µg versus TIO 18 µg was higher than -50 mL (non-inferiority limit).

Secondary: Change from baseline in normalized Area under curve 3 hours post-dose (nAUC0-3/3h) FEV1 of AB/FF 400/12 µg compared to AB 400 µg and and FF 12 µg at Week 24

| | |
|-----------------|--|
| End point title | Change from baseline in normalized Area under curve 3 hours post-dose (nAUC0-3/3h) FEV1 of AB/FF 400/12 µg compared to AB 400 µg and and FF 12 µg at Week 24 |
|-----------------|--|

End point description:

To assess the bronchodilatory effect by evaluating the mean changes from baseline in normalized AUC0-3/3h FEV1 of AB/FF 400/12 µg compared to AB 400 µg and and FF 12 µg after administration of oral inhalation powder BID via DPI to subjects with COPD.

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

End point timeframe:
At baseline and Week 24

| End point values | AB/FF 400/12 µg | AB 400 µg | FF 12 µg | TIO 18 µg |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 273 | 396 | 257 | 398 |
| Units: Litres | | | | |
| least squares mean (standard error) | 0.237 (± 0.013) | 0.162 (± 0.010) | 0.149 (± 0.013) | 0.151 (± 0.010) |

Statistical analyses

| Statistical analysis title | AB/FF 400/12 µg versus AB 400 µg |
|--|-----------------------------------|
| Statistical analysis description: Number of subjects analyzed were 273 in AB/FF 400/12 µg arm and 396 in AB 400 µg arm. | |
| Comparison groups | AB/FF 400/12 µg v AB 400 µg |
| Number of subjects included in analysis | 669 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | LS mean difference |
| Point estimate | 0.075 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.043 |
| upper limit | 0.107 |

| Statistical analysis title | AB/FF 400/12 µg versus FF 12 µg |
|---|-----------------------------------|
| Statistical analysis description: Number of subjects analyzed were 273 in AB/FF 400/12 µg arm and 257 in FF 12 µg arm. | |
| Comparison groups | AB/FF 400/12 µg v FF 12 µg |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed model for repeated measures |
| Parameter estimate | LS mean difference |
| Point estimate | 0.087 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.052 |
| upper limit | 0.122 |

Secondary: Responder (number [%] of subjects) analysis of St. George's Respiratory Questionnaire (SGRQ) total score with AB/FF 400/12 µg versus AB 400 µg and FF 12 µg.

| | |
|-----------------|--|
| End point title | Responder (number [%] of subjects) analysis of St. George's Respiratory Questionnaire (SGRQ) total score with AB/FF 400/12 µg versus AB 400 µg and FF 12 µg. |
|-----------------|--|

End point description:

SGRQ was a standardized self-completed tool used to measure impaired health and perceived well-being ("quality of life") in respiratory diseases. The questionnaire contained 50 items divided into 3 (symptoms, activity and impacts) dimensions. Each of the 3 dimensions of the questionnaire was scored separately in the range from 0 to 100% (score 0 - no impairment and higher score - poorer health). A summary score utilized responses of all items as the total SGRQ score. SGRQ responders were those with a decrease in SGRQ total score of at least 4 units (criterion for minimal meaningful improvement) from baseline.

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

End point timeframe:

At baseline and Week 24

| End point values | AB/FF 400/12 µg | AB 400 µg | FF 12 µg | TIO 18 µg |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 314 | 475 | 319 | 475 |
| Units: Percentages | | | | |
| Yes | 130 | 188 | 128 | 197 |
| Percentages of "Yes" | 48 | 49 | 50 | 51 |
| No | 140 | 195 | 130 | 192 |
| Percentages of "No" | 52 | 51 | 50 | 49 |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | AB/FF 400/12 µg versus AB 400 µg |
|-----------------------------------|----------------------------------|

Statistical analysis description:

Number of subjects analyzed were 314 in AB/FF 400/12 µg arm and 475 in AB 400 µg arm.

| | |
|---|------------------------------|
| Comparison groups | AB/FF 400/12 µg v AB 400 µg |
| Number of subjects included in analysis | 789 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8714 |
| Method | Logistic random-effect model |
| Parameter estimate | Odds ratio |
| Point estimate | 0.96 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 1.51 |

| | |
|---|---------------------------------|
| Statistical analysis title | AB/FF 400/12 µg versus FF 12 µg |
| Statistical analysis description: | |
| Number of subjects analyzed were 314 in AB/FF 400/12 µg arm and 319 in AB 400 µg arm. | |
| Comparison groups | AB/FF 400/12 µg v FF 12 µg |
| Number of subjects included in analysis | 633 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8873 |
| Method | Logistic random-effect model |
| Parameter estimate | Odds ratio |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.58 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of signature of the ICF throughout the treatment period and including the follow-up period (2 weeks after the last study drug administration)

Adverse event reporting additional description:

An adverse event – An undesirable medical condition/deterioration of pre-existing medical condition following/during exposure to pharmaceutical product, whether/not considered causally related to product. An undesirable medical condition - symptoms (e.g. nausea), signs (e.g. tachycardia)/ abnormal investigation results (e.g. laboratory findings)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | AB/FF 400/12 µg |
|-----------------------|-----------------|

Reporting group description:

Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder BID via DPI.

| | |
|-----------------------|-----------|
| Reporting group title | AB 400 µg |
|-----------------------|-----------|

Reporting group description:

Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.

| | |
|-----------------------|----------|
| Reporting group title | FF 12 µg |
|-----------------------|----------|

Reporting group description:

Randomized subjects received orally FF 12 µg inhalation powder BID via DPI.

| | |
|-----------------------|-----------|
| Reporting group title | TIO 18 µg |
|-----------------------|-----------|

Reporting group description:

Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI.

| Serious adverse events | AB/FF 400/12 µg | AB 400 µg | FF 12 µg |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 314 (7.32%) | 41 / 475 (8.63%) | 22 / 319 (6.90%) |
| number of deaths (all causes) | 1 | 1 | 4 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine carcinoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal meningioma benign | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma stage IV | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriosclerosis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicose vein | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Complication associated with device | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |

| | | | |
|---|-----------------|------------------|------------------|
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 7 / 314 (2.23%) | 11 / 475 (2.32%) | 10 / 319 (3.13%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 11 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 1 / 475 (0.21%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Psychiatric disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Anxiety | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Arterial bypass occlusion | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Foreign body | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc injury | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 2 / 475 (0.42%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 314 (0.00%) | 2 / 475 (0.42%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cor pulmonale chronic | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar infarction | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacunar stroke | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 1 / 475 (0.21%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Polycythaemia | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oliguria | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| End stage renal disease | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 314 (1.27%) | 3 / 475 (0.63%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 314 (0.32%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 1 / 319 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 1 / 475 (0.21%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis viral | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 314 (0.00%) | 0 / 475 (0.00%) | 0 / 319 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|--|--|
| Serious adverse events | TIO 18 µg | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 37 / 475 (7.79%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuroendocrine carcinoma | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal meningioma benign | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatic carcinoma stage IV | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arteriosclerosis | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Varicose vein | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Complication associated with device | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 14 / 475 (2.95%) | | |
| occurrences causally related to treatment / all | 0 / 14 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |

| | | | |
|---|-----------------|--|--|
| Anxiety | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Arterial bypass occlusion | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Foreign body | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc injury | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thermal burn | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 3 / 475 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cor pulmonale chronic | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Atrial tachycardia | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 475 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebellar infarction | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lacunar stroke | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sciatica | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Polycythaemia | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------|--|--|
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oliguria | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| End stage renal disease | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 475 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Appendicitis | | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia bacterial | | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Post procedural infection | | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Staphylococcal infection | | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngitis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 475 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis viral | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 475 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | AB/FF 400/12 µg | AB 400 µg | FF 12 µg |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 173 / 314 (55.10%) | 222 / 475 (46.74%) | 178 / 319 (55.80%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 7 / 314 (2.23%) | 8 / 475 (1.68%) | 9 / 319 (2.82%) |
| occurrences (all) | 7 | 8 | 10 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 16 / 314 (5.10%) | 19 / 475 (4.00%) | 17 / 319 (5.33%) |
| occurrences (all) | 27 | 20 | 19 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| Diarrhoea subjects affected / exposed occurrences (all) | 6 / 314 (1.91%) 6 | 9 / 475 (1.89%) 9 | 7 / 319 (2.19%) 7 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary subjects affected / exposed occurrences (all) | 49 / 314 (15.61%) 60 | 79 / 475 (16.63%) 90 | 58 / 319 (18.18%) 74 |
| Dyspnoea subjects affected / exposed occurrences (all) | 6 / 314 (1.91%) 6 | 13 / 475 (2.74%) 18 | 6 / 319 (1.88%) 7 |
| Cough subjects affected / exposed occurrences (all) | 6 / 314 (1.91%) 7 | 7 / 475 (1.47%) 7 | 4 / 319 (1.25%) 4 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 15 / 314 (4.78%) 22 | 7 / 475 (1.47%) 7 | 8 / 319 (2.51%) 12 |
| Arthralgia subjects affected / exposed occurrences (all) | 8 / 314 (2.55%) 9 | 4 / 475 (0.84%) 4 | 3 / 319 (0.94%) 4 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 36 / 314 (11.46%) 42 | 47 / 475 (9.89%) 56 | 39 / 319 (12.23%) 45 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 8 / 314 (2.55%) 9 | 13 / 475 (2.74%) 15 | 7 / 319 (2.19%) 7 |
| Sinusitis subjects affected / exposed occurrences (all) | 8 / 314 (2.55%) 8 | 10 / 475 (2.11%) 10 | 6 / 319 (1.88%) 6 |
| Pneumonia subjects affected / exposed occurrences (all) | 4 / 314 (1.27%) 4 | 1 / 475 (0.21%) 1 | 6 / 319 (1.88%) 6 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 4 / 314 (1.27%) 4 | 5 / 475 (1.05%) 5 | 8 / 319 (2.51%) 8 |

| | | | |
|---|--------------------|--|--|
| Non-serious adverse events | TIO 18 µg | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 241 / 475 (50.74%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 7 / 475 (1.47%) | | |
| occurrences (all) | 9 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 25 / 475 (5.26%) | | |
| occurrences (all) | 31 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 475 (1.47%) | | |
| occurrences (all) | 7 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary | | | |
| subjects affected / exposed | 61 / 475 (12.84%) | | |
| occurrences (all) | 70 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 12 / 475 (2.53%) | | |
| occurrences (all) | 12 | | |
| Cough | | | |
| subjects affected / exposed | 17 / 475 (3.58%) | | |
| occurrences (all) | 19 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 7 / 475 (1.47%) | | |
| occurrences (all) | 8 | | |
| Arthralgia | | | |
| subjects affected / exposed | 8 / 475 (1.68%) | | |
| occurrences (all) | 10 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 64 / 475 (13.47%) | | |
| occurrences (all) | 67 | | |

| | | | |
|---|------------------------|--|--|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 17 / 475 (3.58%) 21 | | |
| Sinusitis subjects affected / exposed occurrences (all) | 7 / 475 (1.47%) 7 | | |
| Pneumonia subjects affected / exposed occurrences (all) | 6 / 475 (1.26%) 6 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 475 (0.63%) 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 01 March 2016 | Protocol version 2.0: - Defined primary objective for Market Access and statistical analysis (Synopsis, Sections 4.1, 5.2, 5.5,5.7, 7.1.1) - Included reference for Bretaris® Genuair® and Bretaris® Genuair® Summary of Product Characteristics (SmPC) (Section 3, list of references) - Corrected doses for Atrovent and specified brand names for US and non-US countries (Synopsis, Sections 5.1, 5.4) - Replaced Visit 8 by follow-up phone call (Section 5.1, 5.3, 6.1) - Added clarification on procedures for the end of treatment (EOT) and end of study (EOS) visits, including 1h post-dose pulmonary function test (PFT) after COPD prescribed treatment (Section 5.1) - Added red blood cells morphology, white blood cells differential and mean corpuscular volume (MCV) in the laboratory assessments (Section 8.4.1) |
| 21 March 2016 | Protocol version 3.0: The collection of IP intake was included in the e-diary (Section 5.1) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported