



Clinical trial results:

A pharmacodynamic, randomised, single dose, cross-over study to compare the bronchodilator effect of a new formulation of Tiotropium DPI versus Spiriva® 18 g Handihaler®

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2019-004095-19 |
| Trial protocol | BG |
| Global end of trial date | 21 October 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 12 July 2021 |
| First version publication date | 12 July 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | TIO-II-19-1 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Laboratoires SMB S.A. |
| Sponsor organisation address | 26-28 rue de la pastorale, brussels, Belgium, 1080 |
| Public contact | Clinical Trial Department, Laboratoires SMB S.A., +32 24114828, DptClinique@smb.be |
| Scientific contact | Clinical Trial Department, Laboratoires SMB S.A., +32 24114828, DptClinique@smb.be |

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 | 12 March 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 October 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 October 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary Objective

- To assess the non-inferiority between Tiotropium DPI capsule 8.8µg and Spiriva® 18µg Handihaler® by measurement of the bronchodilating effect

Protection of trial subjects:

The trial was conducted in compliance with the protocol, with the ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice, Step 5 (CPMP/ICH/135/95) (1), the applicable regulatory requirement(s) based on EU Directive 2001/20/EC (2) and EU GCP Directive (2005/28/EC) (3), and the Declaration of Helsinki (World Medical Association) in its revised edition (Brazil, 2013)

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 03 June 2020 |
| 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 | Bulgaria: 60 |
| Country: Number of subjects enrolled | North Macedonia: 6 |
| Worldwide total number of subjects | 66 |
| EEA total number of subjects | 60 |

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) | 33 |
| From 65 to 84 years | 33 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

The patients were screened within 21 days prior to the randomization. Following all screening procedures, patients who satisfied all of the inclusion/exclusion criteria were randomized. The patients visited the clinic 4 times + one telephone follow-up call. Each visit was separated by a wash-out period of at least 3 days with a maximum of 14 days

Pre-assignment

Screening details:

Obtain a signed informed consent form/Obtain demographic data/Record COPD history/review of prior and concomitant medications/Perform a measurement of pulmonary function/review of the inclusion and exclusion criteria/Perform a 12-lead ECG+Vital sign+laboratory tests/Dispensation of rescue medication

Period 1

| | |
|------------------------------|--|
| Period 1 title | Cross-over phase (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

This study was partly blinded. The blind was maintained only for the two doses of SMB tiotropium DPI formulations.

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | No |
| Arm title | SMB Tiotropium 8.8µg |

Arm description:

SMB Tiotropium 8.8 µg DPI, one capsule a day taken by inhalation via the Vertical-Haler®, containing 10.59 µg of tiotropium bromide anhydrous (equivalent to 8.8 µg of tiotropium base)

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tiotropium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Inhalation use |

Dosage and administration details:

SMB Tiotropium 8.8 µg DPI, one capsule a day taken by inhalation via the Vertical-Haler®, containing 10.59 µg of tiotropium bromide anhydrous (equivalent to 8.8 µg of tiotropium base)

| | |
|------------------|---------------------|
| Arm title | SMB Tiotropim 2.2µg |
|------------------|---------------------|

Arm description:

SMB tiotropium 2.2 µg DPI, one capsule a day taken by inhalation via the Vertical-Haler®, containing 2.64 µg of tiotropium bromide anhydrous (equivalent to 2.2 µg of tiotropium base)

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tiotropium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Inhalation use |

Dosage and administration details:

SMB tiotropium 2.2 µg DPI, one capsule a day taken by inhalation via the Vertical-Haler®, containing 2.64 µg of tiotropium bromide anhydrous (equivalent to 2.2 µg of tiotropium base)

| | |
|------------------|-------------------------|
| Arm title | Spiriva Handihaler 18µg |
|------------------|-------------------------|

Arm description:

Spiriva® Handihaler® 18 µg, one inhalation via the Handihaler®, each inhalation containing 22.5 µg of tiotropium bromide monohydrate (equivalent to 18 µg of tiotropium base)

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Tiotropium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Inhalation use |

Dosage and administration details:

Spiriva® Handihaler® 18 µg, one inhalation via the Handihaler®, each inhalation containing 22.5 µg of tiotropium bromide monohydrate (equivalent to 18 µg of tiotropium base)

| Number of subjects in period 1 | SMB Tiotropium 8.8µg | SMB Tiotropim 2.2µg | Spiriva Handihaler 18µg |
|---------------------------------------|---------------------------------|----------------------------|------------------------------------|
| Started | 66 | 66 | 66 |
| Completed | 63 | 63 | 63 |
| Not completed | 3 | 3 | 3 |
| Consent withdrawn by subject | 2 | 2 | 2 |
| Adverse event, non-fatal | 1 | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Cross-over phase |
|-----------------------|------------------|

Reporting group description:

Sixty-six subjects were included and randomized into 6 sequences groups. All randomized subjects took at least one unit of the study drugs. Three subjects prematurely withdrew from the study and 63 (95.5% of the randomized subjects) completed the study.

| Reporting group values | Cross-over phase | Total | |
|---|------------------|-------|--|
| Number of subjects | 66 | 66 | |
| Age categorical 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) | 33 | 33 | |
| From 65-84 years | 33 | 33 | |
| 85 years and over | 0 | 0 | |
| Age continuous Units: years | | | |
| arithmetic mean | 64.1 | | |
| standard deviation | ± 7.9 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 17 | 17 | |
| Male | 49 | 49 | |

End points

End points reporting groups

| | |
|---|-------------------------|
| Reporting group title | SMB Tiotropium 8.8µg |
| Reporting group description: SMB Tiotropium 8.8 µg DPI, one capsule a day taken by inhalation via the Vertical-Haler®, containing 10.59 µg of tiotropium bromide anhydrous (equivalent to 8.8 µg of tiotropium base) | |
| Reporting group title | SMB Tiotropim 2.2µg |
| Reporting group description: SMB tiotropium 2.2 µg DPI, one capsule a day taken by inhalation via the Vertical-Haler®, containing 2.64 µg of tiotropium bromide anhydrous (equivalent to 2.2 µg of tiotropium base) | |
| Reporting group title | Spiriva Handihaler 18µg |
| Reporting group description: Spiriva® Handihaler® 18 µg, one inhalation via the Handihaler®, each inhalation containing 22.5 µg of tiotropium bromide monohydrate (equivalent to 18 µg of tiotropium base) | |

Primary: Trough FEV1 response

| | |
|---|----------------------|
| End point title | Trough FEV1 response |
| End point description: The bronchodilating effect was evaluated by the trough FEV1 response defined as the change in FEV1 from baseline to FEV1 24h post-dose measurement. | |
| End point type | Primary |
| End point timeframe: Visit 2, visit 3 and visit 4 | |

| End point values | SMB Tiotropium 8.8µg | SMB Tiotropim 2.2µg | Spiriva Handihaler 18µg | |
|--------------------------------------|----------------------|---------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 63 | 63 | 63 | |
| Units: L/sec | | | | |
| arithmetic mean (standard deviation) | 0.091 (± 0.169) | 0.068 (± 0.168) | 0.075 (± 0.193) | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Primary efficacy endpoint analysis |
| Statistical analysis description: The bronchodilating effect will be evaluated by the trough FEV1 response. Trough FEV1 response will be compared between IMPs using a mixed model with sequence, period and IMP as fixed effects, patient within sequence as random effect and period-specific baseline as covariate. LS means will be derived from the model and contrasts between IMP will be calculated. The lower bound of the 95% CI of the contrast between treatments will be compared to the non-inferiority threshold of -0.100 L | |
| Comparison groups | SMB Tiotropium 8.8µg v Spiriva Handihaler 18µg |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.596 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.015 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.041 |
| upper limit | 0.07 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Secondary endpoint analysis (Tio 2.2 vs Tio 8.8) |
|-----------------------------------|--|

Statistical analysis description:

Secondary criteria will be analysed using mixed models for cross-over designs. All IMPs will be compared without reference to a non-inferiority threshold. Estimates of the variable and their standard error will be calculated for each IMP Contrast between all IMPs will be computed and compared to 0. P-value and 95% confidence interval of each difference will be presented without adjustment for multiple comparisons.

| | |
|---|--|
| Comparison groups | SMB Tiotropium 8.8µg v SMB Tiotropim 2.2µg |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.467 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.035 |
| upper limit | 0.076 |

| | |
|---|--|
| Statistical analysis title | Secondary endpoint analysis (Tio 2.2 vs Spiriva) |
| Comparison groups | SMB Tiotropim 2.2µg v Spiriva Handihaler 18µg |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.844 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.005 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.061 |

Secondary: Baseline-adjusted AUC of FEV1 from 0 to 24h

| | |
|-----------------------------|---|
| End point title | Baseline-adjusted AUC of FEV1 from 0 to 24h |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Visit 2, visit3 and visit 4 | |

| End point values | SMB Tiotropium 8.8µg | SMB Tiotropim 2.2µg | Spiriva Handihaler 18µg | |
|--------------------------------------|----------------------|---------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 63 | 63 | 63 | |
| Units: L/sec*h | | | | |
| arithmetic mean (standard deviation) | 3.637 (± 3.425) | 3.216 (± 3.428) | 3.457 (± 4.090) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Secondary endpoint analysis (Tio 2.2 vs Tio 8.8) |
| Comparison groups | SMB Tiotropium 8.8µg v SMB Tiotropim 2.2µg |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.428 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.377 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.562 |
| upper limit | 1.316 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Secondary endpoint analysis (Tio 2.2 vs Spiriva) |
| Comparison groups | Spiriva Handihaler 18µg v SMB Tiotropim 2.2µg |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.705 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.179 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.756 |
| upper limit | 1.113 |

| | |
|---|--|
| Statistical analysis title | Secondary endpoint analysis (Tio 8.8 vs Spiriva) |
| Comparison groups | SMB Tiotropium 8.8µg v Spiriva Handihaler 18µg |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.677 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.198 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.743 |
| upper limit | 1.14 |

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Visit 1 to visit 4

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | SMB Tiotropium 8.8µg |
|-----------------------|----------------------|

Reporting group description:

SMB Tiotropium 8.8 µg DPI, one capsule a day taken by inhalation via the Vertical-Haler®, containing 10.59 µg of tiotropium bromide anhydrous (equivalent to 8.8 µg of tiotropium base)

| | |
|-----------------------|---------------------|
| Reporting group title | SMB Tiotropim 2.2µg |
|-----------------------|---------------------|

Reporting group description:

SMB tiotropium 2.2 µg DPI, one capsule a day taken by inhalation via the Vertical-Haler®, containing 2.64 µg of tiotropium bromide anhydrous (equivalent to 2.2 µg of tiotropium base)

| | |
|-----------------------|-------------------------|
| Reporting group title | Spiriva Handihaler 18µg |
|-----------------------|-------------------------|

Reporting group description:

Spiriva® Handihaler® 18 µg, one inhalation via the Handihaler®, each inhalation containing 22.5 µg of tiotropium bromide monohydrate (equivalent to 18 µg of tiotropium base)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse events superior to the defined threshold (5%) were reported in this study.

| Serious adverse events | SMB Tiotropium 8.8µg | SMB Tiotropim 2.2µg | Spiriva Handihaler 18µg |
|---|----------------------|---------------------|-------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 63 (1.59%) | 0 / 63 (0.00%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Cardiac disorders | | | |
| ARRHYTHMIA | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 63 (1.59%) | 0 / 63 (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 |

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

| Non-serious adverse events | SMB Tiotropium 8.8µg | SMB Tiotropim 2.2µg | Spiriva Handihaler 18µg |
|---|----------------------|---------------------|-------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 63 (0.00%) |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported