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 médications/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