Clinical trial results:
A randomized, double-blind, parallel-group, 26-week study comparing the efficacy and safety of indacaterol (Onbrez® Breezhaler® 150 g o.d.) with salmeterol/fluticasone propionate (Seretide® Accuhaler® 50 g/500 g b.i.d.) in patients with moderate chronic obstructive pulmonary disease.

Summary

EudraCT number	2011-003732-31
Trial protocol	GB NL ES IT
Global end of trial date	13 February 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	CQAB149B2401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01555138
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	13 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the non-inferiority of indacaterol (150 µg o.d.) to salmeterol 50 µg/fluticasone propionate 500 µg b.i.d. as measured by trough forced expiratory volume in one second (trough FEV1) after 12 weeks (Day 85) of treatment in patients with moderate COPD and having had no exacerbations in the previous year. Trough was defined as the mean of the FEV1 measurements at 23 h 10 min and 23 h 45 min post the Day 84 morning dose.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.
At Visit 1, all patients were provided a SABA (salbutamol) MDI which they were instructed to use throughout the study as rescue medication. Nebulized salbutamol was not allowed as rescue medication. Patients were instructed to abstain from taking rescue medication (salbutamol) within 6 h of the start of each visit where spirometry was being performed unless absolutely necessary.

Background therapy: -

Evidence for comparator:

Seretide® Accuhaler® (salmeterol 50 µg/fluticasone propionate 500 µg) b.i.d. was selected as a positive control as it is a marketed FDC comprising a LABA and ICS. Seretide® is widely used by physicians as a maintenance therapy for patients with moderate COPD who do not have a history of frequent or recurrent COPD exacerbations. As in many countries the steroid component of Seretide® is not indicated in this group of patients, and in addition has been shown to contribute to potential side effects and safety issues, the demonstration of noninferiority of indacaterol treatment would offer a needed alternative to the use of this steroidcontaining
treatment.

Actual start date of recruitment	29 February 2012
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	Argentina: 254
Country: Number of subjects enrolled	Colombia: 20
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Mexico: 36
Country: Number of subjects enrolled	Switzerland: 22
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	United Kingdom: 8

Country: Number of subjects enrolled	Italy: 212
Worldwide total number of subjects	581
EEA total number of subjects	248

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)	244
From 65 to 84 years	332
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

In total 81 investigative sites participated in the study, randomizing a total of 581 patients at 32 sites in Argentina, 4 sites in Colombia, 21 sites in Italy, 1 site in Malaysia, 5 sites in Mexico, 3 sites in Netherlands, 7 sites in Spain, 4 sites in Switzerland and 4 sites in the UK.

Pre-assignment

Screening details:

A total of 1038 patients were screened of whom 581 were randomized (293 / indacaterol group and 288 /salmeterol/fluticasone propionate group). There was a 14-day screening period during which patients continued salmeterol 50 µg/fluticasone propionate 500 µg MDDPI and "as needed" salbutamol for baseline diary symptoms and use of rescue medication.

Period 1

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

Blinding implementation details:

This was a double-blind, double-dummy study. The identity of the salmeterol/fluticasone and indacaterol treatments was concealed by double-dummy blinding. A double-dummy design was used because the identity of the study drugs could not be disguised and made to look identical due to their different inhaler devices.

Arms

Are arms mutually exclusive?	Yes
Arm title	Indacaterol

Arm description:

Indacaterol 150 µg capsules once daily for inhalation, delivered via the Novartis single dose dry power inhaler (SDDPI) (Onbrez® Breezhaler®)

Arm type	Experimental
Investigational medicinal product name	Indacaterol
Investigational medicinal product code	QAB149
Other name	Onbrez Breezhaler
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Device training packs were provided to study sites following registration of the center in the IRT system after site initiation, and prior to the first patient at the center attending Visit 1. Patients were trained on the use of the SDDPI and MDDPI and were provided illustrated and written instructions on how to use the devices and how to inhale study medication. Instructions were provided on a leaflet by the investigator.
Patients were instructed to administer their medication at approximately the same time and in the same order each morning.
Patients were carefully instructed to:
• take their indacaterol/placebo medication in the morning only (SDDPI)
• take their salmeterol/fluticasone/placebo medication in the morning and in the evening (MDDPI)
• always take their morning medications in the same order
• record the exact time each dose had taken in the eDiary.
Patients were contacted by center personnel approximately one day prior to clinic visits to reinforce training.

Arm title	Salmeterol/fluticasone propionate

Arm description:

Salmeterol 50 mcg /fluticasone propionate 500 mcg for inhalation delivered via a proprietary multi dose

dry powder inhaler (MDDPI) device (Seretide® Accuhaler®) twice daily (b.i.d.)

Arm type	Active comparator
Investigational medicinal product name	salmeterol/fluticasone
Investigational medicinal product code	
Other name	Seretide Accuhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Device training packs were provided to study sites following registration of the center in the IRT system after site initiation, and prior to the first patient at the center attending Visit 1. Patients were trained on the use of the SDDPI and MDDPI and were provided illustrated and written instructions on how to use the devices and how to inhale study medication. Instructions were provided on a leaflet by the investigator.
Patients were instructed to administer their medication at approximately the same time and in the same order each morning.
Patients were carefully instructed to:
• take their indacaterol/placebo medication in the morning only (SDDPI)
• take their salmeterol/fluticasone/placebo medication in the morning and in the evening (MDDPI)
• always take their morning medications in the same order
• record the exact time each dose had taken in the eDiary.
Patients were contacted by center personnel approximately one day prior to clinic visits to reinforce training

Number of subjects in period 1	Indacaterol	Salmeterol/fluticasone propionate
Started	293	288
Completed	246	250
Not completed	47	38
Adverse event, serious fatal	-	1
Consent withdrawn by subject	16	15
Adverse event, non-fatal	14	14
Administration problems	8	-
Abnormal lab results	1	3
Lost to follow-up	1	-
Protocol deviation	5	3
Lack of efficacy	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Indacaterol
Reporting group description:	
Indacaterol 150 µg capsules once daily for inhalation, delivered via the Novartis single dose dry power inhaler (SDDPI) (Onbrez® Breezhaler®)	
Reporting group title	Salmeterol/fluticasone propionate
Reporting group description:	
Salmeterol 50 mcg /fluticasone propionate 500 mcg for inhalation delivered via a proprietary multi dose dry powder inhaler (MDDPI) device (Seretide® Accuhaler®) twice daily (b.i.d.)	

Reporting group values	Indacaterol	Salmeterol/fluticasone propionate	Total
Number of subjects	293	288	581
Age categorical Units: Subjects			
Adults (40-64 years)	132	112	244
From 65-84 years	159	173	332
85 years and over	2	3	5
Age continuous Units: years			
arithmetic mean	65.3	66.8	
standard deviation	± 8.39	± 8.53	-
Gender categorical Units: Subjects			
Female	89	91	180
Male	204	197	401

End points

End points reporting groups

Reporting group title	Indacaterol

Reporting group description:

Indacaterol 150 µg capsules once daily for inhalation, delivered via the Novartis single dose dry power inhaler (SDDPI) (Onbrez® Breezhaler®)

Reporting group title	Salmeterol/fluticasone propionate

Reporting group description:

Salmeterol 50 mcg /fluticasone propionate 500 mcg for inhalation delivered via a proprietary multi dose dry powder inhaler (MDDPI) device (Seretide® Accuhaler®) twice daily (b.i.d.)

Subject analysis set title	Salmeterol/fluticasone Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol set (PPS) included all patients of the FAS without any major protocol deviations or non-protocol deviations

Subject analysis set title	Indacaterol Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol set (PPS) included all patients of the FAS without any major protocol deviations or non-protocol deviations

Subject analysis set title	Salmeterol/fluticisone Modified Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Clinical Team - Please provide information about why the FAS for Table 14.2-1.1 (source for Table 11-5) is 20 less pts than the FAS in Table 11-1. Is it for the following reason in footnote in Table 14.2-1.1. If so, is there a reason why these were not protocol deviations and why excluded from FAS? Please advise where explanation is for this-cannot locate.
"FEV1 data taken within 6 h of rescue medication was excluded from this analysis, as done for trough data outside 22-25 h
after last morning dose."

Subject analysis set title	Indacterol Modified Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Clinical Team - Please provide information about why the FAS for Table 14.2-1.1 (source for Table 11-5) is 53 less pts than the FAS in Table 11-1. Is it for the following reason in footnote in Table 14.2-1.1. If so, is there a reason why these were not protocol deviations and why excluded from FAS? Please advise where explanation is for this-cannot locate.

"FEV1 data taken within 6 h of rescue medication was excluded from this analysis, as done for trough data outside 22-25 h
after last morning dose."

Primary: Trough forced expiratory volume in one second (FEV1) at 12 weeks (imputed with LOCF):

End point title	Trough forced expiratory volume in one second (FEV1) at 12 weeks (imputed with LOCF):

End point description:

Spirometry conducted to internationally accepted standards. Trough FEV1 defined as the mean of the FEV1 measurements at 23 h 10 min and 23 h 45 min post the Day 84 morning dose. The primary variable (imputed with last observation carried forward) will be analysed using a mixed model for the Per Protocol Set (PPS). The model will contain treatment as a fixed effect with the baseline FEV1 measurement, FEV1 prior to inhalation and FEV1 10-15 min post inhalation of salbutamol (components of reversibility at Visit 1) as covariates.
Analysis Population Description: full analysis set

End point type	Primary

End point timeframe:

12 weeks

End point values	Indacaterol Per Protocol Set	Salmeterol/fluticasone Per Protocol Set	Indacterol Modified Full Analysis Set (FAS)	Salmeterol/fluticisone Modified Full Analysis Set (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	225	237	260	268
Units: Liters				
least squares mean (standard error)				
Trough FEV1	1.584 (± 0.0294)	1.593 (± 0.03)	1.591 (± 0.0276)	1.604 (± 0.0281)

Statistical analyses

Statistical analysis title	Per Protocol Set (PPS) Trough FEV1 (L) at Week 12

Statistical analysis description:

The primary variable (imputed with LOCF) will be analyzed using a mixed model for the Per Protocol Set (PPS). The model will contain treatment as a fixed effect with the baseline FEV1 measurement, FEV1 prior to inhalation and FEV1 10-15 min post inhalation of salbutamol (components of reversibility at Visit 1) as covariates. To reflect the randomization scheme the model will also include smoking status.

Comparison groups	Indacaterol Per Protocol Set v Salmeterol/fluticasone Per Protocol Set
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.002 [2]
Method	Mixed models analysis
Parameter estimate	Least squares mean
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.026
Variability estimate	Standard error of the mean
Dispersion value	0.0179

Notes:

[1] - Clinical, please add any additional comments.

[2] - one-sided

Statistical analysis title	FAS - Superiority Trough FEV1 (L) Week 12

Statistical analysis description:

If non-inferiority of indacaterol with respect to trough FEV1 after 12 weeks treatment is met in the PPS, indacaterol will then be tested for superiority using the FAS. Non-inferiority of indacaterol to salmeterol/fluticasone propionate will be demonstrated if the 95% confidence interval for the mean FEV1 difference of indacaterol minus salmeterol/fluticasone propionate lies entirely to the right of -60 mL. The analysis used for the PPS will be repeated for the Full Analysis Set (FAS).

Comparison groups	Indacterol Modified Full Analysis Set (FAS) v Salmeterol/fluticisone Modified Full Analysis Set (FAS)
Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.409 [3]
Method	Mixed models analysis
Parameter estimate	least squared mean
Point estimate	-0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.046
upper limit	0.019
Variability estimate	Standard error of the mean
Dispersion value	0.0165

Notes:

[3] - two-sided

Secondary: Trough FEV1 (L) at Week 26 (imputed with LOCF): treatment comparisons

End point title	Trough FEV1 (L) at Week 26 (imputed with LOCF): treatment comparisons

End point description:

Trough FEV1 (L) at Week 26 (imputed with LOCF): treatment comparisons.
Trough FEV1 is defined as the average of the 23 h 10 min and the 23 h 45 min values taken in the clinic at Visit 11.

End point type	Secondary

End point timeframe:

26 weeks

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: Liters				
least squares mean (standard error)	1.567 (± 0.0302)	1.569 (± 0.0307)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 (L) at individual time points after 12 weeks treatment: treatment comparisons

End point title	FEV1 (L) at individual time points after 12 weeks treatment: treatment comparisons

End point description:

FEV1 at each time point, for each visit, will be analyzed using the same mixed model as specified for the primary analysis. Least squares means will be displayed by treatment group. Full analysis set was used.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: Liters				
least squares mean (standard error)				
-50 min pre-dose	1.601 (± 0.0281)	1.588 (± 0.0286)		
30 min post-dose	1.667 (± 0.0207)	1.656 (± 0.0208)		
1h post-dose	1.693 (± 0.0285)	1.684 (± 0.0293)		
2h post-dose	1.705 (± 0.0291)	1.708 (± 0.03)		
4h post-dose	1.67 (± 0.0215)	1.699 (± 0.0216)		
23h 10 min post-dose	1.577 (± 0.0277)	1.591 (± 0.0284)		
23h 45 min post-dose	1.597 (± 0.0283)	1.613 (± 0.0291)		
-15 min pre-dose	1.623 (± 0.0282)	1.616 (± 0.287)		
5 min post-dose	1.631 (± 0.0209)	1.613 (± 0.0209)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 (L) at individual time points after 26 weeks treatment: treatment comparisons

End point title	FEV1 (L) at individual time points after 26 weeks treatment: treatment comparisons

End point description:

FEV1 at each time point, for each visit, will be analyzed using the same mixed model as specified for the primary analysis. Least squares means will be displayed by treatment group . Analysis Population Description: Full analysis set

End point type	Secondary

End point timeframe:

26 weeks

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: Liters				
least squares mean (standard error)				
-50 min pre-dose	1.569 (± 0.0301)	1.582 (± 0.0304)		
30 min post-dose	1.67 (± 0.0244)	1.656 (± 0.0244)		
1h post-dose	1.676 (± 0.0317)	1.677 (± 0.0324)		
2h post-dose	1.7 (± 0.0318)	1.693 (± 0.0325)		
4h post-dose	1.664 (± 0.032)	1.663 (± 0.0328)		
23h 10 min post-dose	1.551 (± 0.0305)	1.559 (± 0.031)		
23h 45 min post-dose	1.574 (± 0.313)	1.575 (± 0.0318)		
-15 min pre-dose	1.576 (± 0.0294)	1.595 (± 0.03)		
5 min post-dose	1.63 (± 0.0304)	1.63 (± 0.031)		

Statistical analyses

No statistical analyses for this end point

Secondary: FVC over 26 weeks of treatment

End point title	FVC over 26 weeks of treatment

End point description:

FVC at each time point, for each visit, will be analyzed using the same mixed model as specified for the primary analysis. Least squares means will be displayed by treatment group.
Analysis Population Description: Full analysis set

End point type	Secondary

End point timeframe:

12 and 26 weeks

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: Liters				
least squares mean (standard error)				
12 weeks	3.09 (± 0.0457)	3.064 (± 0.0466)		
26 weeks	3.057 (± 0.0512)	3.062 (± 0.052)		

Statistical analyses

No statistical analyses for this end point

Secondary: Analysis of AUC (5 min – 4 h) for FEV1 (L) at Week 12 and Week 26: treatment comparison

End point title	Analysis of AUC (5 min – 4 h) for FEV1 (L) at Week 12 and Week 26: treatment comparison

End point description:

The standardized (with respect to the length of time) AUC for FEV1 will be calculated between 5 min and 4 h post morning dose as the sum of trapezoids divided by the length of time at Day 84 (Visit 6) and Day 182 (Visit 10). Scheduled (not actual) time points are to be used. FEV1 measurements taken within 6 h of rescue use will be set to missing before the standardized AUC is calculated Analysis Population Description: Full analysis set

End point type	Secondary

End point timeframe:

12 and 26 weeks

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: Liters				
least squares mean (standard error)				
12 weeks	1.689 (± 0.0201)	1.689 (± 0.0203)		
26 weeks	1.683 (± 0.0304)	1.682 (± 0.031)		

Statistical analyses

No statistical analyses for this end point

Secondary: Transition Dyspnea Index (TDI) total score at Week 12 and Week 26: treatment comparisons

End point title	Transition Dyspnea Index (TDI) total score at Week 12 and Week 26: treatment comparisons

End point description:

The Transition Dyspnea Index (TDI) total score after 12 and 26 weeks of treatment will be analyzed using the same mixed model as specified for the primary analysis with the Baseline Dyspnea Index (BDI) total score as the baseline.Total score ranging - 9 to + 9. The lower the score, the more deterioration in severity of dyspnea. One additional option in each category, which does not contribute to the score, allows for circumstances in which impairment is due to reasons other than dyspnea.

End point type	Secondary

End point timeframe:

12 and 26 weeks

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: Units on a scale				
least squares mean (standard error)				
12 weeks	1.89 (± 0.499)	1.69 (± 0.509)		
26 weeks	2.58 (± 0.543)	2.7 (± 0.552)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of COPD exacerbations per patient over 26 weeks: treatment comparisons (without imputation; Full analysis set)

End point title	Number of COPD exacerbations per patient over 26 weeks: treatment comparisons (without imputation; Full analysis set)

End point description:

The number of exacerbations during the 26 week treatment period will be analyzed using a generalized linear model assuming a negative binomial distribution.

End point type	Secondary

End point timeframe:

26 weeks

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: participants				
None	233	215		
One	47	57		
Two	11	15		
Three	2	1		

Greater than or equal to four	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean daily number of puffs of rescue medication used over 26 weeks of treatment

End point title	Mean daily number of puffs of rescue medication used over 26 weeks of treatment

End point description:

The mean daily number of puffs of rescue medication taken by the patient will be derived. If the number of puffs is missing for part of the day (either morning or evening) then a half day will be used in the denominator. Rescue medication data recorded during the 14 day run-in period will be used to calculate the baseline. The mean change from baseline in the daily number of puffs of rescue medication will be analyzed using the same mixed model as specified for the primary analysis, with the baseline FEV1 replaced with the baseline daily rescue use.

End point type	Secondary

End point timeframe:

26 weeks

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: number of puffs				
arithmetic mean (standard deviation)				
Baseline	1.82 (± 2.274)	1.83 (± 2.035)		
Baseline Week 12	1.73 (± 2.06)	1.83 (± 2.05)		
Week 12	1.5 (± 1.883)	1.45 (± 1.697)		
Baseline week 26	1.73 (± 2.06)	1.88 (± 2.028)		
Week 26	1.37 (± 1.775)	1.37 (± 1.678)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of days with no rescue medication use

End point title	Percentage of days with no rescue medication use

End point description:

A ‘day with no rescue use’ is defined from diary data as any day where the patient has taken no puffs of rescue medication. The percentage of ‘days with no rescue use’ will be derived and analyzed as for the percentage of ‘nights with no nighttime awakenings’.
Analysis Population Description: Full Analysis Set

End point type	Secondary
End point timeframe: 26 weeks	

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: Days				
least squares mean (standard error)	52.8 (± 3.71)	54.6 (± 3.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: St Georges Respiratory Questionnaire for COPD

End point title	St Georges Respiratory Questionnaire for COPD

End point description:

A Total and three component scores are calculated: Symptoms; Activity; Impacts. Each component of the questionnaire is scored separately:The score for each component is calculated separately by dividing the summed weights by the maximum possible weight for that component and expressing the result as a percentage: Score = 100 x Summed weights from all positive items in that component divided by Sum of weights for all items in that component The Total score is calculated in similar way: Score = 100 x Summed weights from all positive items in the questionnaire divided by Sum of weights for all items in the questionnaire Sum of maximum possible
weights for each component and Total: Symptoms 566.2 Activity 982.9 Impacts 1652.8 Total (sum of maximum for all three components) 3201.9 The proportion of patients who achieve a clinically important improvement of at least 4 units in the total SGRQ will be analyzed. The higher the score the more symptoms of disease are present. Analysis Populati

End point type	Secondary
End point timeframe: 12 and 26 weeks	

End point values	Indacaterol	Salmeterol/fluticasone propionate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	288		
Units: numbers on a scale				
least squares mean (standard error)				
12 weeks	32.8 (± 1.58)	32.9 (± 1.61)		
26 weeks	33.1 (± 1.87)	33.5 (± 1.93)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Salmeterol/Fluticasone 50mcg/500mcg
Reporting group description:	
Salmeterol/Fluticasone 50mcg/500mcg	
Reporting group title	Indacaterol 150 mcg
Reporting group description:	
Indacaterol 150 mcg	

Serious adverse events	Salmeterol/Fluticasone 50mcg/500mcg	Indacaterol 150 mcg	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 288 (5.90%)	5 / 293 (1.71%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neurilemmoma benign			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric cancer			

subjects affected / exposed	0 / 288 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 288 (0.69%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 288 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Duodenitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 288 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 288 (1.04%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 288 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 288 (0.69%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Salmeterol/Fluticasone 50mcg/500mcg	Indacaterol 150 mcg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 288 (29.51%)	70 / 293 (23.89%)	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	71 / 288 (24.65%)	60 / 293 (20.48%)	
occurrences (all)	89	75	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 288 (6.25%)	15 / 293 (5.12%)	
occurrences (all)	22	15	

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