Sponsor

Novartis

Generic Drug Name

Indacaterol/ QAB149

Trial Indication(s)

Chronic obstructive pulmonary disease (COPD)

Protocol Number

CQAB149B2401

Protocol Title

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

Clinical Trial Phase

Phase IV

Phase of Drug Development

Phase IV

Study Start/End Dates

29-Feb-2012 (First Patient First Visit) to 13-Feb-2014 (Last Patient Last Visit)

Reason for Termination (If applicable)

N/A

Study Design/Methodology

This was a parallel group, 26 week, randomized, double blind, double dummy, multi-center, non-inferiority study to compare the efficacy and safety of indacaterol 150 µg o.d. with salmeterol 50 µg/fluticasone propionate 500 µg b.i.d. in patients with moderate (Stage II) COPD who on entry to the study were being treated with salmeterol 50 µg/fluticasone propionate 500 µg multi-dose dry powder inhaler (MDDPI).

Patients underwent a screening period of 14 days before they were randomized (Visit 2, Day 1) in a 1:1 ratio to receive either inhaled indacaterol 150 µg o.d. and a placebo device to salmeterol/fluticasone propionate or salmeterol 50 µg/fluticasone propionate 500 µg b.i.d. and a placebo device to indacaterol for a treatment period of 26-weeks. The randomization was stratified overall and in the subgroup of patients undergoing inspiratory capacity assessments by smoking status (current/ex-smoker).

Centers

81 sites in 9 countries: Argentina (32), Colombia (4), Italy (21), Malaysia (1), Mexico (5), Netherlands (3), Spain (7), Switzerland (4), United Kingdom(4)

Publication

None

Objectives:

Primary Objective:

The Primary objective: 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 year before entry into the study. Trough is defined as the mean of the FEV1 measurements at 23 h 10 min and 23 h 45 min post the Day 84 morning dose.

Secondary Objectives:

1. To evaluate the effect of indacaterol 150 µg o.d. as compared to salmeterol/fluticasone propionate 50 µg/500 µg b.i.d. on trough FEV_1 at multiple, pre-defined visits
2. To evaluate the effect of indacaterol 150 µg o.d. as compared to salmeterol/fluticasone propionate 50 µg/500 µg b.i.d. on standardized $FEV_1AUC_{5\ min-\ 4\ h}$ at Weeks 12 and 26 (Days 84 and 182, respectively)
3. To evaluate the effect of indacaterol 150 µg o.d. as compared to salmeterol/fluticasone propionate 50 µg/500 µg b.i.d. on FEV_1 and FVC at multiple, pre-defined, scheduled time points
4. To evaluate the effect of indacaterol 150 µg o.d. as compared to salmeterol/fluticasone propionate 50 µg/500 µg b.i.d. on the total score of the Transition Dyspnea Index (TDI) at Weeks 12 and 26 of treatment
5. To evaluate the effect of indacaterol 150 µg o.d. as compared to salmeterol/fluticasone propionate 50 µg/500 µg b.i.d. on the total score of the St George's Respiratory Questionnaire for COPD Patients (SGRQ-C) at Weeks 12 and 26 of treatment
6. To evaluate the effect of indacaterol 150 µg o.d. as compared to salmeterol/fluticasone propionate 50 µg/500 µg b.i.d. on the mean number of puffs of rescue medication use, and percentage of days without rescue medication use over the 26-week treatment period
7. To evaluate the effect of indacaterol 150 µg o.d. as compared to salmeterol/fluticasone propionate 50 µg/500 µg b.i.d. on COPD exacerbations over the 26-week treatment period
8. To evaluate the effect of indacaterol 150 µg o.d. as compared to salmeterol/fluticasone propionate 50 µg/500 µg b.i.d. on safety in terms of adverse events, ECG, laboratory parameters (hematology, biochemistry and urinalysis), and vital signs over the 26-week treatment period.

Test Product (s), Dose(s), and Mode(s) of Administration

Investigational therapy

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

Reference therapy

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

Statistical Methods

Four sets were defined for analysis: the randomized set, the full analysis set (FAS), the per-protocol set (PPS) and the safety set. The primary analysis set for efficacy was PPS. The FAS was used for supportive analysis of the primary objective and for the analysis of all other efficacy variables. The safety set was used in the analysis of all safety variables. The number of patients in each analysis set was summarized by treatment group and in total.

The primary variable was "Trough FEV_1" after 12 weeks of treatment (measured at Visit 7 [Day 85]) with trough being defined as the average of the 23 h 10 min and the 23 h 45 min values taken in the clinic on Day 85. The primary variable (imputed with last observation carried forward [LOCF]) was analyzed using a mixed model for the PPS. The model included treatment as a fixed effect with the baseline FEV_1 measurement, FEV_1 prior to inhalation and FEV_1 10-15 min post inhalation of salbutamol (components of SABA reversibility at Visit 1) as covariates. To reflect the randomization scheme the model also included the baseline smoking status (current/ex-smoker) and country as fixed effects with center nested within country as a random effect.

Estimates of least squares means and the estimate of the treatment contrast for indacaterol 150 µg minus salmeterol 50 µg /fluticasone propionate 500 µg were displayed along with the associated 95% confidence interval (CI).

Non-inferiority of indacaterol to salmeterol/fluticasone propionate was demonstrated if the 95% CI for the mean FEV_1 difference of indacaterol minus salmeterol/fluticasone propionate lies entirely to the right of (higher than) -60 mL.

Supportive analyses were performed for the FAS with trough FEV_1 at Week 12 imputed with LOCF and for the FAS and PPS without imputation with LOCF.

Other secondary efficacy variables were summarized and using the similar mixed model as specified for the primary analysis for the FAS only. No adjustment for multiplicity was made.

All safety data was summarized for the safety set. Subgroup analyses by age group (<65 years / ≥65 years) and by sex was performed for AEs. All treatment emergent adverse events, including COPD exacerbations, were summarized and listed.

For all of the laboratory data (hematology and biochemistry) minimum/maximum values were summarized with standard descriptive statistics including changes from baseline and with shift tables of frequencies (n (%) of patients) relative to the normal ranges between baseline and worst post-baseline values. The number of patients with abnormal urinalysis dipstick result was also summarized. Furthermore, notable criteria were defined for selected laboratory tests based on FDA guidelines. The number of patients with newly occurring or worsening clinically notable laboratory values was summarized by parameter and treatment. All laboratory data was listed with values outside normal ranges flagged. All clinically notable values were listed separately. To evaluate potential drug-induced liver injury, the numbers of patients with newly occurring or worsening elevations in liver function tests at any time post-baseline were summarized.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

1. Male and female adults aged ≥40 years, who had signed an Informed Consent Form prior to initiation of any study-related procedure
2. Outpatients with moderate COPD (Stage II) as classified by the GOLD Guidelines, 2010:

- Post-bronchodilator FEV_1 <80% and ≥50% of the predicted normal value at Visit 1 (Day -14)
- Post-bronchodilator FEV_1/FVC <70% at Visit 1 (Day -14). Post-bronchodilator refers to 10-15 min after inhalation of 400 µg (4x100 µg) salbutamol
- Where FEV_1 post bronchodilator value was less than the FEV_1 pre-bronchodilator value, patients were asked to return for a repeat assessment no earlier than the following morning, and no later than within a few days. If two consecutive

post bronchodilator values of FEV_1 were less than the corresponding pre-bronchodilator FEV_1 values, the patient were not allowed to proceed in this study

3. Able to perform spirometry assessments in accordance with ATS/ERS criteria for acceptability and repeatability
4. Current or ex-smokers who had a smoking history of at least 10 pack years (e.g., 10 pack years = 1 pack /day x 10 years, or ½ pack/day x 20 years). An ex-smoker was defined as a subject who had not smoked for ≥6 months at Visit 1
5. On treatment with the FDC of salmeterol 50 µg/fluticasone propionate 500 µg MDDPI b.i.d. for the treatment of COPD for ≥3 months directly preceding Visit 1
6. Able to use an electronic patient diary
7. Able to use a single dose dry powder inhaler (SDDPI), a multi-dose dry powder inhaler (MDDPI), and a pressurized MDI (rescue medication – salbutamol); and comply with the study regimen

Key exclusion criteria:

1. patients who had had a COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the one year prior to Visit 1 or during the period between Visit 1 and Visit 2
2. patients with a history of, or current clinically significant, in the opinion of the investigator, ECG abnormality
3. patients with any medical condition or significant laboratory abnormality which might compromise patient safety, interfere with evaluations, or preclude completion of the study
4. patients who had had a respiratory tract infection within 4 weeks prior to Visit 1, or developing a respiratory tract infection between Visit 1 and Visit 2
5. patients requiring long-term oxygen therapy prescribed for >12 h per day
6. patients with any history of asthma, or onset of respiratory symptoms prior to age 40 years
7. patients with any concomitant pulmonary disease or active pulmonary tuberculosis
8. patients with allergic rhinitis and using a H1- antagonist or intra-nasal corticosteroids intermittently
9. patients with a diagnosis of α-1 anti-trypsin deficiency

10. patients participating in or planning to initiate an evolving or changing phase of a supervised pulmonary rehabilitation program during the study;
11. patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the inhaled drugs such as long and short acting beta-2 agonists, inhaled steroids, sympathomimetic amines, lactose, gelatin or any of the other excipients or drugs of a similar class or any component thereof
12. patients with evidence (upon visual inspection) of oropharyngeal candidiasis at Visit 1 or Visit 2
13. patients not meeting all concomitant medication requirements as specified in accordance with all protocol requirement
14. patients using other investigational drugs (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever was longer

Participant Flow Table

Patient disposition (All patients)

	Ind 150 µg n (%)	S+F n (%)	Total n (%)
Patients			
Screened	-	-	1038
Randomized	293 (100)	288 (100)	581 (100)
Exposed	293 (100)	288 (100)	581 (100)
Completed	246 (84.0)	250 (86.8)	496 (85.4)
Discontinued	47 (16.0)	38 (13.2)	85 (14.6)
Primary reason for premature discontinuation			
Subject withdrew consent	16 (5.5)	15 (5.2)	31 (5.3)
Adverse event(s)	14 (4.8)	14 (4.9)	28 (4.8)
Administrative problems	8 (2.7)	0	8 (1.4)
Protocol deviation	5 (1.7)	3 (1.0)	8 (1.4)
Unsatisfactory therapeutic effect	2 (0.7)	2 (0.7)	4 (0.7)
Abnormal test procedure result(s)	1 (0.3)	3 (1.0)	4 (0.7)
Lost to follow-up	1 (0.3)	0	1 (0.2)
Death*	0	1 (0.3)	1 (0.2)

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

Patients who have screen failed and re-screened under a new patient number will be counted twice in the number of screening.

* There is a discrepancy between one patient who died during the study in the 'Patient Disposition Table' and the 'Deaths, other serious adverse events (including COPD exacerbations) and adverse events leading to permanent discontinuation of study drug Table'. In one it is considered death and in the other discontinuation due to AE (sudden death was considered a type of AE).The tables were derived from different sources.

Baseline Characteristics

Demographic summary (Safety set)

		Ind 150 µg N=293	S+F N=288	Total N=581
Age (years)	n	293	288	581
	Mean	65.3	66.8	66.0
	SD	8.39	8.53	8.49
	Median	66.0	67.0	66.0
	Min - Max	41-88	41-88	41-88
Age group - n (%)	40 - 64 years	132 (45.1)	112 (38.9)	244 (42.0)
	≥65 years	161 (54.9)	176 (61.1)	337 (58.0)
Sex - n (%)	Male	204 (69.6)	197 (68.4)	401 (69.0)
	Female	89 (30.4)	91 (31.6)	180 (31.0)
Race - n (%)	Caucasian	252 (86.0)	252 (87.5)	504 (86.7)
	Asian	2 (0.7)	1 (0.3)	3 (0.5)
	Native American	22 (7.5)	21 (7.3)	43 (7.4)
	Other	17 (5.8)	14 (4.9)	31 (5.3)
Weight (kg)	n	285	282	567
	Mean	74.9	77.6	76.2
	SD	14.09	15.59	14.90
	Median	74.0	76.5	75.0
	Min - Max	39.0-123.6	44.0-136.5	39.0-136.5
Height (cm)	n	285	282	567
	Mean	166	166	166
	SD	8.8	8.6	8.7
	Median	166	166	166
	Min – Max	145-189	144-190	144-190
BMI (kg/m^2)	n	285	282	567
	Mean	27.1	28.1	27.6
	SD	4.62	5.15	4.91
	Median	26.7	27.3	27.0
	Min – Max	14.5-43.4	16.3-51.0	14.5-51.0
BMI group (kg/m^2)	≤30.0	214 (73.0)	199 (69.1)	413 (71.1)
	>30.0	71 (24.2)	83 (28.8)	154 (26.5)

	Ind 150 µg N=293	S+F N=288	Total N=581
Missing	8 (2.7)	6 (2.1)	14 (2.4)

Ind=Indacaterol
S+F= Salmeterol 50 µg/fluticasone 500 µg
BMI=body mass index

Summary of Efficacy

Primary Outcome Result(s)

Trough FEV_1 (L) at Week 12 (imputed with Last Observation Carried Forward): treatment comparisons (Per-protocol and full analysis set)

	Treatment				Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Per protocol set **Comparisons for non-inferiority**								
Ind 150 µg (N=247)	225	1.584	0.0294	Ind 150 µg - S+F	-0.009	0.0179	(-0.045, 0.026)	0.002* (one-sided)
S+F (N=249)	237	1.593	0.0300					
Full analysis set **Comparisons for superiority**								
Ind 150 µg (N=293)	260	1.591	0.0276	Ind 150 µg - S+F	-0.014	0.0165	(-0.046, 0.019)	0.409 (two-sided)
S+F (N=288)	268	1.604	0.0281					

Ind=Indacaterol
S+F= Salmeterol 50 µg/fluticasone 500 µg

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.

Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center (country), with center (country) as a random effect.

A hierarchical testing approach was taken: If indacaterol was demonstrated to be non-inferior to S+F (95% confidence interval lay entirely to the right of (higher than) -0.060 L) for the per protocol set then the superiority was evaluated for the full analysis set. Superiority was demonstrated if the two-sided p-value was less than 0.05 and the 95% confidence interval lay entirely to the right of (higher than) 0 L.

* denotes a statistical significant comparison according to the hierarchical testing procedure.

Secondary Outcome Result(s)

Trough FEV_1 (L) at Week 26 (imputed with Last Observation Carried Forward): treatment comparisons (Full analysis set)

	Treatment				Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Ind 150 µg (N=293)	242	1.567	0.0302	Ind 150 µg - S+F	-0.002	0.0179	(-0.037, 0.034)	0.926
S+F (N=288)	245	1.569	0.0307					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.

Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status +country + center (country), with center (country) as a random effect.

Trough FEV_1 was defined as the average of the 23 h 10 min and the 23 h 45 min FEV_1 values at Day 183.

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

Analysis of AUC (5 min – 4 h) for FEV_1 (L) at Week 12 and Week 26: treatment comparison (Full analysis set)

		Treatment			Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Week 12								
Ind 150 µg (N=293)	244	1.689	0.0201	Ind 150 µg - S+F	0.000	0.0168	(-0.033, 0.033)	0.999

		Treatment			Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
S+F (N=288)	245	1.689	0.0203					
Week 26								
Ind 150 µg (N=293)	232	1.683	0.0304	Ind 150 µg - S+F	0.001	0.0186	(-0.035, 0.038)	0.949
S+F (N=288)	232	1.682	0.0310					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.

Mixed model: AUC = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center (country), with center (country) as a random effect, with center as a random effect.

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

FEV_1 (L) at individual time points after 12 weeks treatment: treatment comparisons (Full analysis set)

		Treatment			Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
-50 min pre-dose								
Ind 150 µg (N=293)	249	1.601	0.0281	Ind 150 µg - S+F	0.013	0.0174	(-0.021, 0.048)	0.438
S+F (N=288)	246	1.588	0.0286					
-15 min pre-dose								
Ind 150 µg (N=293)	251	1.623	0.0282	Ind 150 µg - S+F	0.006	0.0173	(-0.028, 0.040)	0.717
S+F (N=288)	247	1.616	0.0287					
5 min post-dose								
Ind 150 µg (N=293)	242	1.631	0.0209	Ind 150 µg - S+F	0.018	0.0170	(-0.015, 0.052)	0.286
S+F (N=288)	248	1.613	0.0209					

	Treatment				Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
30 min post-dose								
Ind 150 µg (N=293)	242	1.667	0.0207	Ind 150 µg - S+F	0.011	0.0173	(-0.023, 0.045)	0.511
S+F (N=288)	246	1.656	0.0208					
1h post-dose								
Ind 150 µg (N=293)	248	1.693	0.0285	Ind 150 µg - S+F	0.009	0.0173	(-0.025, 0.043)	0.611
S+F (N=288)	248	1.684	0.0293					
2h post-dose								
Ind 150 µg (N=293)	240	1.705	0.0291	Ind 150 µg - S+F	-0.003	0.0181	(-0.038, 0.033)	0.878
S+F (N=288)	242	1.708	0.0300					
4h post-dose								
Ind 150 µg (N=293)	231	1.670	0.0215	Ind 150 µg - S+F	-0.029	0.0178	(-0.064, 0.006)	0.105
S+F (N=288)	235	1.699	0.0216					
23h 10 min post-dose								
Ind 150 µg (N=293)	244	1.577	0.0277	Ind 150 µg - S+F	-0.014	0.0169	(-0.048, 0.019)	0.390
S+F (N=288)	242	1.591	0.0284					
23h 45 min post-dose								
Ind 150 µg (N=293)	249	1.597	0.0283	Ind 150 µg - S+F	-0.016	0.0173	(-0.050, 0.018)	0.346
S+F (N=288)	243	1.613	0.0291					

LSM = least squares mean, SE = standard error of the mean, CI = confidence interval.

Mixed model: FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center (country) + error, with center (country) included as random effect.

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

FEV_1 (L) at individual time points after 26 weeks treatment: treatment comparisons (Full analysis set)

	Treatment				Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
-50 min pre-dose								
Ind 150 µg (N=293)	231	1.569	0.0301	Ind 150 µg - S+F	-0.013	0.0185	(-0.049, 0.024)	0.492
S+F (N=288)	236	1.582	0.0304					
-15 min pre-dose								
Ind 150 µg (N=293)	236	1.576	0.0294	Ind 150 µg - S+F	-0.020	0.0180	(-0.055, 0.016)	0.277
S+F (N=288)	236	1.595	0.0300					
5 min post-dose								
Ind 150 µg (N=293)	234	1.630	0.0304	Ind 150 µg - S+F	0.001	0.0186	(-0.036, 0.037)	0.971
S+F (N=288)	234	1.630	0.0310					
30 min post-dose								
Ind 150 µg (N=293)	235	1.670	0.0244	Ind 150 µg - S+F	0.014	0.0186	(-0.023, 0.050)	0.463
S+F (N=288)	235	1.656	0.0244					
1h post-dose								
Ind 150 µg (N=293)	231	1.676	0.0317	Ind 150 µg - S+F	-0.001	0.0194	(-0.039, 0.037)	0.951

	Treatment				Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
S+F (N=288)	235	1.677	0.0324					
2h post-dose								
Ind 150 µg (N=293)	228	1.700	0.0318	Ind 150 µg - S+F	0.007	0.0199	(-0.032, 0.046)	0.710
S+F (N=288)	225	1.693	0.0325					
4h post-dose								
Ind 150 µg (N=293)	222	1.664	0.0320	Ind 150 µg - S+F	0.001	0.0198	(-0.038, 0.040)	0.972
S+F (N=288)	220	1.663	0.0328					
23h 10 min post-dose								
Ind 150 µg (N=293)	226	1.551	0.0305	Ind 150 µg - S+F	-0.008	0.0187	(-0.045, 0.028)	0.654
S+F (N=288)	227	1.559	0.0310					
23h 45 min post-dose								
Ind 150 µg (N=293)	236	1.574	0.0313	Ind 150 µg - S+F	-0.001	0.0186	(-0.038, 0.035)	0.956
S+F (N=288)	236	1.575	0.0318					

LSM = least squares mean, SE = standard error of the mean, CI = confidence interval.

Mixed model: FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center (country) + error, with center (country) included as random effect.

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

Summary Statistics of Trough FVC over 26 weeks of treatment (Full analysis set)

Ind 150 ug N=293	S+F N=288

Visit	Statistic	Base	Post	Change	% Change	Base	Post	Change	% Change
Day 29	n	151	151	151	151	153	153	153	153
	Mean	2.997	2.992	-0.005	0.45	2.997	2.960	-0.038	-1.20
	SD	0.7942	0.8003	0.3042	10.967	0.7750	0.8385	0.3223	11.293
	Min	1.320	1.439	-0.805	-26.68	1.183	1.258	-0.887	-30.94
	Q25	2.392	2.349	-0.186	-6.00	2.449	2.327	-0.213	-7.44
	Median	2.959	2.893	-0.011	-0.30	2.914	2.919	-0.041	-1.12
	Q75	3.594	3.597	0.155	4.75	3.530	3.524	0.112	3.78
	Max	5.029	5.103	0.752	41.64	4.940	5.402	1.172	47.87
Day 57	n	151	151	151	151	146	146	146	146
	Mean	3.035	3.036	0.001	0.58	3.078	3.020	-0.058	-1.90
	SD	0.8384	0.8437	0.3138	10.995	0.7877	0.8340	0.3196	10.774
	Min	1.320	1.326	-1.096	-35.38	1.183	1.312	-1.235	-37.76
	Q25	2.396	2.384	-0.173	-6.13	2.540	2.464	-0.216	-7.43
	Median	2.982	2.988	0.016	0.37	2.994	2.983	-0.051	-1.69
	Q75	3.600	3.642	0.206	6.95	3.578	3.629	0.110	3.17
	Max	5.204	5.439	0.792	29.92	4.976	5.233	0.956	32.32

		Ind 150 ug N=293				S+F N=288			
Visit	Statistic	Base	Post	Change	% Change	Base	Post	Change	% Change
Day 84	n	172	172	172	172	161	161	161	161
	Mean	3.020	3.000	-0.021	-0.35	3.025	2.960	-0.065	-1.99
	SD	0.8273	0.8533	0.3203	11.266	0.7781	0.7972	0.2760	9.126
	Min	1.320	1.513	-1.267	-40.91	1.283	1.346	-0.970	-27.51
	Q25	2.394	2.311	-0.184	-6.34	2.481	2.363	-0.219	-6.64
	Median	2.944	2.928	-0.012	-0.54	2.894	2.806	-0.054	-1.99
	Q75	3.558	3.494	0.143	5.10	3.530	3.480	0.103	3.37
	Max	5.321	5.187	1.032	41.07	5.153	5.358	0.689	24.21
Day 85	n	252	252	252	252	255	255	255	255
	Mean	3.023	3.023	0.000	0.18	3.021	3.012	-0.010	-0.36
	SD	0.8166	0.8446	0.2981	10.183	0.8219	0.8941	0.3308	10.867
	Min	1.320	1.106	-0.981	-27.23	1.183	1.068	-0.930	-30.52
	Q25	2.412	2.431	-0.171	-6.11	2.356	2.358	-0.182	-5.93
	Median	2.951	2.940	-0.030	-1.17	2.924	2.936	-0.031	-1.04
	Q75	3.584	3.580	0.183	5.86	3.538	3.592	0.147	5.70

		Ind 150 ug N=293				S+F N=288			
Visit	Statistic	Base	Post	Change	% Change	Base	Post	Change	% Change
	Max	5.413	5.374	0.955	29.75	5.190	6.177	1.608	52.03
Day 85 (LOCF)	n	260	260	260	260	268	268	268	268
	Mean	3.028	3.025	-0.003	0.11	3.027	3.000	-0.026	-0.89
	SD	0.8145	0.8404	0.2977	10.207	0.8149	0.8844	0.3375	11.063
	Min	1.320	1.106	-0.981	-27.23	1.183	1.068	-0.930	-30.52
	Q25	2.420	2.431	-0.174	-6.30	2.423	2.361	-0.207	-6.61
	Median	2.951	2.927	-0.034	-1.21	2.949	2.932	-0.031	-1.32
	Q75	3.584	3.580	0.178	5.65	3.542	3.544	0.139	4.90
	Max	5.413	5.374	0.955	29.75	5.190	6.177	1.608	52.03
Day 182	n	161	161	161	161	146	146	146	146
	Mean	3.042	3.019	-0.023	-0.65	3.026	2.968	-0.058	-1.83
	SD	0.8415	0.8773	0.3318	11.272	0.7622	0.8015	0.3179	10.691
	Min	1.320	1.207	-1.047	-30.60	1.497	1.148	-0.748	-28.44
	Q25	2.400	2.373	-0.223	-7.58	2.471	2.378	-0.246	-8.74
	Median	2.981	2.943	-0.035	-1.21	2.909	2.911	-0.085	-3.01
	Q75	3.585	3.627	0.151	4.69	3.570	3.494	0.132	4.62
	Max	5.204	5.419	0.994	36.96	4.847	5.096	1.016	28.10

		Ind 150 ug N=293				S+F N=288			
Visit	Statistic	Base	Post	Change	% Change	Base	Post	Change	% Change
Day 183	n	239	239	239	239	243	243	243	243
	Mean	3.024	2.963	-0.061	-1.81	3.027	2.975	-0.052	-1.56
	SD	0.8083	0.8266	0.3253	10.870	0.8212	0.8612	0.3416	11.057
	Min	1.320	1.341	-1.013	-28.47	1.183	1.235	-1.061	-41.31
	Q25	2.406	2.346	-0.270	-9.81	2.356	2.358	-0.236	-8.30
	Median	2.948	2.889	-0.060	-1.95	2.910	2.862	-0.052	-1.69
	Q75	3.585	3.478	0.126	4.45	3.538	3.555	0.130	4.82
	Max	5.413	5.173	0.947	40.02	5.190	5.601	1.603	41.34
Day 183 (LOCF)	n	242	242	242	242	245	245	245	245
	Mean	3.024	2.965	-0.059	-1.80	3.032	2.981	-0.051	-1.53
	SD	0.8145	0.8386	0.3254	10.893	0.8193	0.8601	0.3408	11.027

Min	1.320	1.207	-1.013	-28.47	1.183	1.235	-1.061	-41.31
Q25	2.406	2.346	-0.270	-9.81	2.357	2.362	-0.234	-8.27
Median	2.949	2.890	-0.055	-1.92	2.914	2.862	-0.052	-1.69
Q75	3.585	3.478	0.133	4.50	3.546	3.555	0.130	4.82
Max	5.413	5.173	0.947	40.02	5.190	5.601	1.603	41.34

Base = Baseline, Change = Post baseline - baseline, % Change = 100 * Change / Base.
Only patients with a value at both baseline and the respective post-baseline visit were included.
Trough FVC was defined as the average of the 23 h 10 min and the 23 h 45 min FVC values at Day 85 and Day 183.
At all other post-baseline visits, trough FVC was defined as the average of the -50 min and -15 min FVC values.
Baseline was defined as the average of the -50 min and -15 min FVC values taken at Visit 2 prior to first dose.
If both values were missing (or not confirmed to be before the morning dose), then the pre-bronchodilator measurement taken at the screening visit was used as baseline.
FVC 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.

TDI focal score at Week 12 and Week 26: treatment comparisons (Full analysis set)

	Treatment				Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Week 12								
Ind 150 µg (N=293)	249	1.89	0.499	Ind 150 µg - S+F	0.20	0.265	(-0.32, 0.72)	0.446
S+F (N=288)	249	1.69	0.509					
Week 26								
Ind 150 µg (N=293)	233	2.58	0.543	Ind 150 µg - S+F	-0.12	0.302	(-0.71, 0.48)	0.694
S+F (N=288)	235	2.70	0.552					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
BDI = Baseline Dyspnea Index, TDI = Transition Dyspnea Index.

Mixed model: TDI = treatment + BDI + FEV_1 reversibility components + smoking status +country + center (country), with center (country) as a random effect.

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

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

	Ind 150 µg N=293	S+F N=288
Number of exacerbations per patient (without imputation) - n (%)		
None	233 (79.5)	215 (74.7)
1	47 (16.0)	57 (19.8)
2	11 (3.8)	15 (5.2)
3	2 (0.7)	1 (0.3)
≥4	0	0
Total number of exacerbations	75	90
Total number of treatment years	131.78	134.67
Rate of exacerbations per year	0.57	0.67
Treatment comparison Ind 150 µg vs. S+F (without imputation)		
Ratio of rates	0.86	
95% CI	(0.62,1.20)	
p-value	0.367	

CI = confidence interval.

Treatment group comparisons are based on a generalized linear model assuming a negative binomial distribution with fixed effects of treatment, smoking status, country, FEV_1 reversibility components.

As the offset variable log (days of treatment duration) was used.

Ratio of rates <1 favors the treatment group in the numerator of the ratio.

Malaysia was pooled together with Colombia as if one country and Netherlands/Great Britain together as if another, due to model convergence issues.

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

Rescue medication use over 26 weeks: treatment comparisons (Full analysis set)

Treatment				Treatment difference				
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Change from baseline in the mean daily number of puffs of rescue medication								
Ind 150 µg (N=293)	268	-0.44	0.192	Ind 150 µg - S+F	0.05	0.115	(-0.17, 0.28)	0.650
S+F (N=288)	272	-0.49	0.197					
Change from baseline in the mean daytime number of puffs of rescue medication								
Ind 150 µg (N=293)	259	-0.23	0.074	Ind 150 µg - S+F	0.03	0.063	(-0.09, 0.15)	0.616
S+F (N=288)	258	-0.26	0.074					
Change from baseline in the mean nighttime number of puffs of rescue medication								
Ind 150 µg (N=293)	266	-0.19	0.095	Ind 150 µg - S+F	0.03	0.057	(-0.09, 0.14)	0.658
S+F (N=288)	265	-0.21	0.097					
Percentage of 'days with no rescue use'								
Ind 150 µg (N=293)	256	52.8	3.71	Ind 150 µg - S+F	-1.8	2.74	(-7.2, 3.6)	0.505
S+F (N=288)	262	54.6	3.68					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.

Mixed model: change from baseline (or % of days) = treatment + baseline number of puffs (or baseline % of days) + FEV_1 reversibility components + smoking status + country + center (country) + error, with center (country) included as random effect.

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

SGRQ-C total score at Week 12 and Week 26: treatment comparisons (Full analysis set)

	Treatment				Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Week 12								
Ind 150 µg (N=293)	255	32.8	1.58	Ind 150 µg - S+F	-0.1	0.94	(-1.9, 1.8)	0.927
S+F (N=288)	257	32.9	1.61					
Week 26								
Ind 150 µg (N=293)	238	33.1	1.87	Ind 150 µg - S+F	-0.4	1.04	(-2.5, 1.6)	0.693
S+F (N=288)	242	33.5	1.93					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.

Mixed model: SGRQ-C total score = treatment + baseline SGRQ-C total score + FEV_1 reversibility components + smoking status + country + center (country) + error, with center (country) included as random

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

Summary of Safety

Safety Results

Adverse events (including COPD exacerbations) overall and by primary system organ class - n (%) of patients (Safety set)

	Ind 150 µg N=293 n (%)	S+F N=288 n (%)
Patients with any AE(s)	131 (44.7)	154 (53.5)
Primary system organ class		

	Ind 150 µg N=293 n (%)	S+F N=288 n (%)
Respiratory, thoracic and mediastinal disorders	76 (25.9)	83 (28.8)
Infections and infestations	62 (21.2)	76 (26.4)
Musculoskeletal and connective tissue disorders	13 (4.4)	13 (4.5)
Gastrointestinal disorders	9 (3.1)	16 (5.6)
General disorders and administration site conditions	9 (3.1)	8 (2.8)
Nervous system disorders	9 (3.1)	8 (2.8)
Injury, poisoning and procedural complications	6 (2.0)	7 (2.4)
Vascular disorders	6 (2.0)	6 (2.1)
Eye disorders	5 (1.7)	1 (0.3)
Investigations	3 (1.0)	2 (0.7)
Skin and subcutaneous tissue disorders	3 (1.0)	4 (1.4)
Cardiac disorders	2 (0.7)	9 (3.1)
Psychiatric disorders	2 (0.7)	2 (0.7)
Blood and lymphatic system disorders	1 (0.3)	2 (0.7)
Ear and labyrinth disorders	1 (0.3)	3 (1.0)
Endocrine disorders	1 (0.3)	1 (0.3)
Hepatobiliary disorders	1 (0.3)	5 (1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	3 (1.0)
Renal and urinary disorders	1 (0.3)	5 (1.7)
Reproductive system and breast disorders	1 (0.3)	1 (0.3)
Immune system disorders	0	2 (0.7)
Metabolism and nutrition disorders	0	1 (0.3)

Primary system organ classes are sorted in descending order of frequency in the Ind 150 µg treatment group.
Only treatment emergent adverse events are summarized.
Ind=Indacaterol
S+F= Salmeterol 50 µg/fluticasone 500 µg

Most frequent AEs, including COPD exacerbations, (at least 5% in any treatment group) by preferred term - n (%) of patients (Safety set)

	Ind 150 µg N=293 n (%)	S+F N=288 n (%)
Patients with any AE(s)	131 (44.7)	154 (53.5)
Preferred term		
Chronic obstructive pulmonary disease	60 (20.5)	73 (25.3)
Nasopharyngitis	15 (5.1)	18 (6.3)

Preferred terms are sorted in descending order of frequency in the Ind 150 µg treatment group.
Only treatment emergent adverse events are summarized. The first row includes AEs of all frequencies.
Ind=Indacaterol
S+F= Salmeterol 50 µg/fluticasone 500 µg

Deaths, other serious adverse events (including COPD exacerbations) and adverse events leading to permanent discontinuation of study drug – n (%) of patients (Safety set)

	Ind 150 µg N=293 n (%)	S+F N=288 n (%)
Deaths*	0	2 (0.7)
Patients with any AE(s)	131 (44.7)	154 (53.5)
Serious AEs or AE discontinuations		
SAEs	5 (1.7)	17 (5.9)
Discontinued due to AE(s)*	14 (4.8)	15 (5.2)
Discontinued due to SAE(s)	3 (1.0)	7 (2.4)
Discontinued due to non-SAE(s)	11 (3.8)	8 (2.8)

A patient could have discontinued study treatment due to both a SAE and a non-SAE.

* There is a discrepancy between one patient who died during the study in the 'Patient Disposition Table' and the 'Deaths, other serious adverse events (including COPD exacerbations) and adverse events leading to permanent discontinuation of study drug Table'. In one it is considered death and in the other discontinuation due to AE (sudden death was considered a type of AE).The tables were derived from different sources (CMP and AEV eCFR pages)

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

Serious AEs, including COPD exacerbations, by primary system organ class and preferred term - n (%) of patients (Safety set)

	Ind 150 µg N=293 n (%)	S+F N=288 n (%)
Patients with any serious AE(s)	5 (1.7)	17 (5.9)
Primary system organ class and preferred term		
Blood and lymphatic system disorders	0	2 (0.7)
Anemia	0	1 (0.3)
Thrombocytopenia	0	1 (0.3)
Cardiac disorders	1 (0.3)	5 (1.7)
Cardiac failure	1 (0.3)	0
Atrial fibrillation	0	2 (0.7)
Bradycardia	0	1 (0.3)
Coronary artery disease	0	1 (0.3)
Supraventricular tachycardia	0	1 (0.3)
Gastrointestinal disorders	1 (0.3)	1 (0.3)
Pancreatitis acute	1 (0.3)	0
Duodenitis	0	1 (0.3)
Dyspepsia	0	1 (0.3)
General disorders and administration site conditions	0	2 (0.7)
Non-cardiac chest pain	0	1 (0.3)
Sudden death	0	1 (0.3)
Hepatobiliary disorders	0	2 (0.7)

	Ind 150 µg N=293 n (%)	S+F N=288 n (%)
Cholelithiasis	0	1 (0.3)
Cholestasis	0	1 (0.3)
Infections and infestations	0	2 (0.7)
Pneumonia	0	2 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	3 (1.0)
Gastric cancer	1 (0.3)	0
Mesothelioma	0	1 (0.3)
Neurilemmoma benign	0	1 (0.3)
Renal cancer	0	1 (0.3)
Nervous system disorders	0	1 (0.3)
Transient ischemic attack	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (0.7)	3 (1.0)
Chronic obstructive pulmonary disease	1 (0.3)	3 (1.0)
Pneumothorax spontaneous	1 (0.3)	0
Vascular disorders	0	2 (0.7)
Peripheral arterial occlusive disease	0	1 (0.3)
Peripheral artery thrombosis	0	1 (0.3)

Primary system organ classes are sorted alphabetically; preferred terms are sorted within each primary system organ class in descending order of frequency in the Ind 150 µg treatment group.

Ind=Indacaterol

S+F= Salmeterol 50 µg/fluticasone 500 µg

Other Relevant Findings

None

Conclusion:

The study met its aims, demonstrating that patients with moderate airflow limitation and no exacerbations in the prior 12 months can be switched from salmeterol/fluticasone to indacaterol, with no loss of efficacy.

Date of Clinical Trial Report

02-JUL-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

10-FEB-2015

Date of Latest Update

Reason for Update

New Record