Sponsor

Novartis

Generic Drug Name

Indacaterol

Therapeutic Area of Trial

Chronic obstructive pulmonary disease

Approved Indication

- Investigational

Study Number

CQAB149B2212

Title

A randomized, double-blind, double-dummy, active (formoterol 12 µg b.i.d) and placebo controlled, multicenter, 5 period crossover, dose-ranging study to assess the bronchodilatory efficacy and safety of single doses of indacaterol 150 µg, 300 µg and 600 µg delivered via single dose dry powder inhaler (SDDPI) vs. placebo in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Phase of Development

Phase IIb

Study Start/End Dates

31-Oct-2006 – 31 Jan 2007

Study Design/Methodology

This study was of a 5 period crossover design. A 14 day run-in period (Visit 1 to 2) was used to confirm patients were stable on allowable COPD therapy. At Visit 2, patients whose eligibility was confirmed were randomized to one of 5 treatment sequences and entered the first of five double-blind double-dummy 1 day treatment periods. Patients received a different 1 day treat-

ment at Visits 2, 4, 6, 8 and 10 according to their treatment sequence: one of 3 doses of indacaterol 150, 300, or 600 µg (o.d); formoterol 12 µg (b.i.d); or placebo.

Patients were assessed on the day of each treatment and also returned for further assessments the following day (approx 23 h post dose). After each treatment patients entered a minimum 6 day wash-out period during which they received allowable COPD treatment and short-acting β_2-agonist rescue medication.

Centres

9 centres, Belgium

Publication

On-going

Objectives

Primary objective(s)

This was to assess the bronchodilatory efficacy of single doses of indacaterol 150 µg, 300 µg & 600 µg via SDDPI in patients with moderate to severe COPD as compared to placebo in terms of 24 h post-dose (trough) FEV_1.

Secondary objective(s)

These were to assess the safety of single doses of indacaterol 150 µg, 300 µg & 600 µg via SDDPI compared to placebo in patients with COPD in terms of adverse events, laboratory analysis, vital signs (blood pressure and pulse rate) and ECGs, and to evaluate the bronchodilatory efficacy measures of single doses of indacaterol 150 µg, 300 µg and 600 µg via SDDPI compared to placebo in terms of:

- Time to peak FEV_1
- Percent change in FEV_1 compared to baseline at each time point post-dose
- FEV_1 and FVC at each time point post-dose
- standardized $AUC_{30\,min\,-\,4\,hours}$ FEV_1

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

Indacterol 150, 300 and 600 µg delivered by Single dose dry powder inhaler (SDDPI; 150 and 300 µg capsules).

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

Formoterol 12 µg delivered via the Aerolizer and placebo to both active agents with the appropriate inhaler device.

Criteria for Evaluation

Primary variables

This was to assess the bronchodilatory efficacy of single doses of indacaterol 150 µg, 300 µg & 600 µg via SDDPI in patients with moderate to severe COPD as compared to placebo in terms of 24 h post-dose (trough) FEV_1

Secondary variables

These were to evaluate the bronchodilatory efficacy measures of single doses of indacaterol 150 µg, 300 µg and 600 µg via SDDPI compared to placebo in terms of:

- Time to peak FEV_1
- Percent change in FEV_1 compared to baseline at each time point post-dose
- FEV_1 and FVC at each time point post-dose
- Standardized FEV_1 AUC between 30 min and 4 h post-dose

Safety and tolerability

To assess the safety of single doses of indacaterol 150 µg, 300 µg & 600 µg via SDDPI compared to placebo in patients with COPD in terms of adverse events, laboratory analysis, vital signs (blood pressure and pulse rate) and ECGs, and Body weight

Pharmacology

The serum PK parameters C_{max}, t_{max}, and AUC_{0-24} were determined from the individual concentration-time data from noncompartmental analysis using WinNonlin Professional v5.01 software.

Other

Statistical Methods

The modified intention-to-treat (mITT) population included all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment they received. All efficacy variables, including the primary efficacy variables, were analyzed on the modified intent-to-treat population. The per-protocol (PP) population included all patients in the mITT population without any major protocol violations. The safety population included all patients who received at least one dose of study drug.

Efficacy evaluation

The primary variable, 24-hour trough in FEV_1 following inhalation of study drug, was summarized by treatment for the mITT population. The comparison of indacaterol 150 µg or 300 µg or 600 µg to placebo was evaluated by testing the following null hypothesis (Ho) versus the alternative hypothesis (Ha) using the mITT population:

Ho: There is no difference in the trough FEV_1 for patients with COPD treated with indacaterol compared to placebo

Ha: There is a difference in the trough FEV_1 for patients with COPD treated with indacaterol compared to placebo

Two sided hypothesis testing was based on the following 3 main contrasts:

Indacaterol 600µg versus placebo

Indacaterol 300µg versus placebo

Indacaterol 150µg versus placebo

Each contrast described above was tested, and an adjustment for multiple comparisons was made using a stepwise Dunnett test implemented in a closed test procedure. The family-wise error rate was fixed at 0.05.

Twenty-four hour trough FEV_1 data was modeled using an Analysis of Covariance (ANCOVA), with patient, period, and treatment group as fixed effects, and the (period) baseline FEV_1 as covariates. Here the (period) baseline FEV_1 was defined as the average of 2 values taken at -50 and -15 minutes before study drug administration in that treatment period. For the trough in FEV_1, adjusted means for each treatment group and the estimated treatment differences for indacaterol 150 µg, 300 µg or 600 µg versus placebo were presented. Associated simultaneous 95% confidence intervals (based on a single step Dunnett procedure) and multiplicity adjusted 2 sided p-values (using the stepwise Dunnett procedure) were derived for the contrasts.

For the trough in FEV_1, if one of the 23h 10min or 23h 45min values was missing at Visits 3, 5, 7, 9 or 11 then the remaining non-missing value was taken as the trough in FEV_1. If both values were missing, or if the patient had withdrawn from the trial, regardless of the reason for discontinuation, then the trough in FEV_1 was regarded as missing and the patient was not included in the analysis.

If any of the values used in the trough FEV_1 were collected within six hours of rescue medication or outside of the window (22h 25m, 24h 30m) then the individual FEV_1 value was set to missing and the imputation rules stated above were then applied.

The primary analysis was repeated with the same ANCOVA model and multiplicity adjustments

for the PP population. The primary analysis was repeated with the same ANCOVA model and multiplicity adjustments using the log transformed trough FEV_1 for both the mITT population and the PP population. Analysis results without the multiplicity adjustment were provided for all pairwise comparisons of the 5 treatment groups for the trough FEV_1 (mITT and PP) and for the log transformed trough FEV_1 (mITT).

Secondary and Exploratory Efficacy Evaluation

No multiplicity adjustment was made for each of the comparisons between indacaterol dose and placebo in secondary endpoints. Area Under the Curve (AUC) for FEV_1 was determined for 30 minutes to 4 hours and then (all the post dose time points in the range 0 to 4 hours) standardized with respect to time. This was a change from the originally planned analysis, in which (AUC) for FEV_1 from pre-dose to 4 hours was to be calculated. The response variable, standardized AUC(30 min–4 hr) FEV_1, was modeled using an ANCOVA model, with patient, period, and treatment group as fixed effects, and the (period) baseline FEV_1 values as covariates (mITT population). The (period) baseline FEV_1 was defined as the average of 2 measurements taken 50 and 15 minutes prior to inhalation of study drug in each period. There were no carryover terms in the models. The adjusted standardized AUC(30 min–4 hr) FEV_1 means and the estimates of treatment contrasts of interest, associated P-values and 95% confidence intervals of those contrasts were presented.

For each time point, an ANCOVA model was fitted for FVC with patient, period, and treatment group as fixed effects, and the (period) baseline FVC values as covariates (mITT population). The (period) baseline FVC was defined as the average of 2 measurements taken 50 and 15 minutes prior to inhalation of study drug in each period. For FVC the adjusted means, the estimates of all treatment contrasts, the associated P-values, and 95% confidence intervals were presented at each time point. No imputation was done for missing FVC results at any post-baseline time point.

FEV_1 Percent Change in FEV_1, and Time to Peak FEV_1 (calculated in minutes from the time of inhalation of study drug to the 4 hours post-dose time point) were analyzed separately at each time point in a manner similar to FVC. Each analysis was performed using an ANCOVA with patient, period, and treatment group as fixed effects, and the (period) baseline FEV_1 values as covariates (mITT population). The (period) baseline FEV_1 was defined as the average of 2 measurements taken 50 and 15 minutes prior to inhalation of study drug in each period. The adjusted means, the estimates of all treatment contrasts, the associated P-values, and 95% confidence intervals were presented at each time point. No imputation was done for missing FEV_1 results at any post-baseline time point.

An exploratory comparison of indacaterol 150 µg, 300 µg and 600 µg treatments with each other and active control, and active control with placebo, for the primary endpoint, was performed using the same ANCOVA model described for the primary efficacy endpoint. Estimated treatment differences were displayed along with the associated 95% confidence intervals and p-values (2 sided). The same exploratory analysis was made for each of the secondary efficacy endpoints as well.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Male and females aged 40-75 years with COPD and symptoms such as cough, sputum production, and shortness of breath.
- Smoking history of at least 10 pack years
- FEV1 less than 65% of the predicted normal value and at least 0.75 L
- Pre-bronchodilator FEV1/FVC less than 70%

Exclusion Criteria:

- A history of asthma or COPD diagnosis before the age of 40
- Hospitalization for COPD exacerbation within the previous 6 weeks
- Respiratory tract infection within 6 weeks
- Use of long-term oxygen therapy
- Diabetes type I or uncontrolled diabetes type II
- Clinically relevant laboratory abnormality or clinically significant condition
- Corrected QT interval (QTc) above 430 ms for males and 450 ms for females, or a history of QTc prolongation.

Other protocol-defined inclusion/exclusion criteria may apply.

Number of Subjects

Patient disposition – n (%) of patients

Total no. of patients	Total n (%)
Screened	70
Randomized	51 (100%)
Completed	47 (92.2%)
Discontinued	4 (7.8%)
Reasons for discontinuation:	
Adverse Event(s)	2 (3.9%)
Unsatisfactory therapeutic effect	2 (3.9%)
Last treatment before discontinuation	
Indacaterol 600mcg	1 (2.0%)
Formoterol 12mcg	1 (2.0%)
Placebo	2 (3.9%)

Number of randomized patients is denominator for percentages

Demographic and Background Characteristics

Variable		Statistic	Total N=51
Age (years)		Mean (SD)	61.8 (8.20)
		Range	43 - 73
Age distribution (years)	40-64	n (%)	30 (58.8)
	65-75	n (%)	21 (41.2)
Sex	Male	n (%)	44 (86.3)
	Female	n (%)	7 (13.7)
Race	Caucasian	n (%)	51 (100.0)
Height (cm)		Mean (SD)	170.4 (7.11)
		Range	156 - 186
Weight (kg)		Mean (SD)	75.17 (15.820)
		Range	50.0 - 120.0
Body mass index (kg/m^2)		Mean (SD)	25.788 (4.5794)
		Range	17.17 - 39.89
Duration of COPD (years)		Mean (SD)	9.645 (7.5770)
		Range	0.02 - 31.91
FEV_1 before inhalation of salbutamol at Visit 1 (L)		Mean (SD)	1.335 (0.3458)
		Range	0.78 - 2.00
FEV_1 before inhalation of salbutamol at Visit 1		Mean (SD)	44.622 (11.2662)
(% predicted FEV_1)		Range	22.22 - 64.71
FEV_1 after inhalation of salbutamol at Visit 1 (L)		Mean (SD)	1.520 (0.3975)
		Range	0.72 - 2.33

FEV_1 after inhalation of salbutamol at Visit 1		Mean	50.6 (12.2)
(% predicted FEV_1)		Range	26.6-72.0
FEV_1 reversibility (% increase of FEV_1)*		Mean (SD)	14.977 (16.3256)
		Range	-32.99 - 57.76
FVC at Visit 1 (L)		Mean (SD)	2.856 (0.6093)
		Range	1.66 - 3.94
Smoking History	Never smoked	n (%)	0 (-)
	Ex-smoker	n (%)	28 (54.9)
	Current smoker	n (%)	23 (45.1)

*% increase in FEV_1 within 30 minutes after inhalation of salbutamol from FEV_1 before inhalation of salbutamol.

Primary Objective Result(s)

Analysis of covariance of 24 h post-dose (trough) FEV_1 (L) (modified ITT population)

	n	LSMean	SE	95% CI*	p-value*	SS 95% CI**	SD p-value (2-sided)**
Treatment Effect							
Indacaterol 600 µg	50	1.46	0.014	(1.43, 1.49)			
Indacaterol 300 µg	49	1.45	0.015	(1.42, 1.48)			
Indacaterol 150 µg	47	1.42	0.015	(1.39, 1.45)			
Formoterol 12 µg	50	1.41	0.014	(1.38, 1.43)			
Placebo	48	1.28	0.015	(1.25, 1.31)			
Treatment Contrast (Primary Analysis)							
Indacaterol 600 µg-Placebo		0.18	0.021	(0.14, 0.22)	<0.001	(0.13, 0.23)	<0.001
Indacaterol 300 µg-Placebo		0.17	0.020	(0.13, 0.21)	<0.001	(0.12, 0.22)	<0.001
Indacaterol 150 µg-Placebo		0.14	0.020	(0.10, 0.18)	<0.001	(0.09, 0.19)	<0.001
Treatment Contrast (Secondary / Exploratory Analysis)							
Indacaterol 600 µg-300 µg		0.01	0.020	(-0.03, 0.05)	0.5690		
Indacaterol 600 µg-150 µg		0.04	0.020	(0.00, 0.08)	0.0428		
Indacaterol 600 µg-Formoterol 12 µg		0.05	0.020	(0.01, 0.09)	0.0089		
Indacaterol 300 µg-150 µg		0.03	0.020	(-0.01, 0.07)	0.1382		
Indacaterol 300 µg-Formoterol 12 µg		0.04	0.020	(0.00, 0.08)	0.0426		
Indacaterol 150 µg-Formoterol 12 µg		0.01	0.020	(-0.03, 0.05)	0.5925		
Formoterol 12 µg-Placebo		0.13	0.020	(0.09, 0.17)	<0.001		

*95% CIs and p-values are calculated without multiplicity adjustment

** SS 95% CIs are based on a single step Dunnett procedure implemented using % SimIntervals SAS macro. The SD p-values are based on stepdown Dunnett procedure implemented using % SimTests SAS macro

Secondary Objective Result(s)

Analysis of covariance of time to peak FEV1 (min) (mITT population)

Treatment effect / contrast	n	Time to peak FEV_1 (min) LSMean	SE	95% CI	p-value (2-sided)
Indacaterol 600 µg	50	137.28	10.415	(116.73, 157.82)	
Indacaterol 300 µg	49	123.41	10.772	(102.16, 144.66)	
Indacaterol 150 µg	47	116.28	10.987	(94.60, 137.96)	
Formoterol 12 µg	50	145.92	10.480	(125.25, 166.60)	
Placebo	49	119.11	11.000	(97.41, 140.81)	
Indacaterol 600 µg - Placebo		18.16	15.173	(-11.77, 48.10)	0.2328
Indacaterol 300 µg - Placebo		4.30	14.855	(-25.01, 33.61)	0.7726
Indacaterol 150 µg - Placebo		-2.83	15.094	(-32.61, 26.95)	0.8515
Formoterol 12 µg - Placebo		26.81	15.120	(-3.02, 56.64)	0.0778
Indacaterol 600 µg - 300 µg		13.87	15.030	(-15.79, 43.52)	0.3574
Indacaterol 600 µg - 150 µg		21.00	15.174	(-8.94, 50.93)	0.1681
Indacaterol 600 µg - Formoterol 12 µg		-8.65	14.783	(-37.82, 20.52)	0.5592
Indacaterol 300 µg - 150 µg		7.13	15.035	(-22.53, 36.79)	0.6359
Indacaterol 300 µg - Formoterol 12 µg		-22.52	14.931	(-51.97, 6.94)	0.1333
Indacaterol 150 µg - Formoterol 12 µg		-29.64	15.084	(-59.40, 0.11)	0.0509

Analysis of covariance of FEV_1 (L) by time point (mITT population)

Time point: 30 min

Treatment effect / contrast	n	FEV_1 (L) LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	49	1.50	0.014	(1.48, 1.53)	
QAB149 300mcg	49	1.52	0.014	(1.49, 1.54)	
QAB149 150mcg	47	1.48	0.014	(1.46, 1.51)	
Formoterol 12mcg	50	1.50	0.014	(1.47, 1.52)	
Placebo	49	1.33	0.014	(1.30, 1.35)	
QAB149 600mcg - Placebo		0.18	0.020	(0.14, 0.22)	<.001
QAB149 300mcg - Placebo		0.19	0.019	(0.15, 0.23)	<.001
QAB149 150mcg - Placebo		0.16	0.020	(0.12, 0.20)	<.001
Formoterol 12mcg - Placebo		0.17	0.020	(0.13, 0.21)	<.001
QAB149 600mcg - 300mcg		-0.01	0.020	(-0.05, 0.03)	0.5584
QAB149 600mcg - 150mcg		0.02	0.020	(-0.02, 0.06)	0.2880
QAB149 600mcg - Formoterol 12mcg		0.01	0.019	(-0.03, 0.05)	0.6579
QAB149 300mcg - 150mcg		0.03	0.020	(-0.01, 0.07)	0.0963
QAB149 300mcg - Formoterol 12mcg		0.02	0.019	(-0.02, 0.06)	0.3012
QAB149 150mcg - Formoterol 12mcg		-0.01	0.020	(-0.05, 0.03)	0.5230

Time point: 1 hour

Treatment effect / contrast	n	FEV_1 (L) LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	1.54	0.015	(1.51, 1.57)	
QAB149 300mcg	49	1.54	0.015	(1.51, 1.57)	
QAB149 150mcg	47	1.46	0.016	(1.43, 1.49)	
Formoterol 12mcg	50	1.52	0.015	(1.49, 1.55)	
Placebo	49	1.35	0.016	(1.32, 1.38)	
QAB149 600mcg - Placebo		0.19	0.022	(0.15, 0.23)	<.001
QAB149 300mcg - Placebo		0.19	0.021	(0.15, 0.23)	<.001
QAB149 150mcg - Placebo		0.11	0.022	(0.07, 0.16)	<.001
Formoterol 12mcg - Placebo		0.17	0.022	(0.13, 0.22)	<.001
QAB149 600mcg - 300mcg		0.00	0.022	(-0.04, 0.04)	0.9128
QAB149 600mcg - 150mcg		0.08	0.022	(0.03, 0.12)	<.001
QAB149 600mcg - Formoterol 12mcg		0.02	0.021	(-0.03, 0.06)	0.4716
QAB149 300mcg - 150mcg		0.08	0.022	(0.04, 0.12)	<.001
QAB149 300mcg - Formoterol 12mcg		0.02	0.021	(-0.02, 0.06)	0.4107
QAB149 150mcg - Formoterol 12mcg		-0.06	0.022	(-0.10, -0.02)	0.0054

Time point: 2 hours

Treatment effect / contrast	n	FEV_1 (L) LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	1.59	0.014	(1.55, 1.60)	
QAB149 300mcg	49	1.56	0.014	(1.53, 1.59)	
QAB149 150mcg	47	1.50	0.014	(1.47, 1.53)	
Formoterol 12mcg	50	1.56	0.014	(1.53, 1.59)	
Placebo	49	1.32	0.014	(1.30, 1.35)	
QAB149 600mcg - Placebo		0.25	0.020	(0.21, 0.29)	<.001
QAB149 300mcg - Placebo		0.24	0.020	(0.20, 0.27)	<.001
QAB149 150mcg - Placebo		0.17	0.020	(0.13, 0.21)	<.001
Formoterol 12mcg - Placebo		0.23	0.020	(0.19, 0.27)	<.001
QAB149 600mcg - 300mcg		0.02	0.020	(-0.02, 0.05)	0.4470
QAB149 600mcg - 150mcg		0.08	0.020	(0.04, 0.12)	<.001
QAB149 600mcg - Formoterol 12mcg		0.02	0.019	(-0.02, 0.06)	0.3458
QAB149 300mcg - 150mcg		0.06	0.020	(0.02, 0.10)	0.0017
QAB149 300mcg - Formoterol 12mcg		0.00	0.020	(-0.04, 0.04)	0.8662
QAB149 150mcg - Formoterol 12mcg		-0.06	0.020	(-0.10, -0.02)	0.0030

Time point: 4 hours

Treatment effect / contrast	n	FEV_1 (L) LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	1.57	0.014	(1.54, 1.60)	
QAB149 300mcg	49	1.56	0.015	(1.53, 1.59)	
QAB149 150mcg	47	1.48	0.015	(1.45, 1.51)	
Formoterol 12mcg	50	1.53	0.015	(1.50, 1.55)	
Placebo	49	1.33	0.015	(1.30, 1.36)	
QAB149 600mcg - Placebo		0.24	0.021	(0.20, 0.28)	<.001
QAB149 300mcg - Placebo		0.24	0.021	(0.20, 0.28)	<.001
QAB149 150mcg - Placebo		0.15	0.021	(0.11, 0.19)	<.001
Formoterol 12mcg - Placebo		0.20	0.021	(0.16, 0.24)	<.001
QAB149 600mcg - 300mcg		0.01	0.021	(-0.04, 0.05)	0.8067
QAB149 600mcg - 150mcg		0.09	0.021	(0.05, 0.13)	<.001
QAB149 600mcg - Formoterol 12mcg		0.04	0.020	(0.00, 0.08)	0.0327
QAB149 300mcg - 150mcg		0.09	0.021	(0.05, 0.13)	<.001
QAB149 300mcg - Formoterol 12mcg		0.04	0.021	(0.00, 0.08)	0.0611
QAB149 150mcg - Formoterol 12mcg		-0.05	0.021	(-0.09, -0.01)	0.0221

Time point: 23 hours 10 min

FEV_1 (L)

Treatment effect / contrast	n	LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	1.45	0.016	(1.42, 1.48)	
QAB149 300mcg	49	1.44	0.016	(1.41, 1.48)	
QAB149 150mcg	47	1.41	0.017	(1.38, 1.45)	
Formoterol 12mcg	50	1.41	0.016	(1.38, 1.44)	
Placebo	48	1.27	0.017	(1.24, 1.30)	
QAB149 600mcg - Placebo		0.18	0.023	(0.14, 0.23)	<.001
QAB149 300mcg - Placebo		0.17	0.023	(0.13, 0.22)	<.001
QAB149 150mcg - Placebo		0.14	0.023	(0.10, 0.19)	<.001
Formoterol 12mcg - Placebo		0.14	0.023	(0.09, 0.18)	<.001
QAB149 600mcg - 300mcg		0.01	0.023	(-0.04, 0.05)	0.7463
QAB149 600mcg - 150mcg		0.04	0.023	(-0.01, 0.08)	0.0917
QAB149 600mcg - Formoterol 12mcg		0.04	0.023	(0.00, 0.09)	0.0494
QAB149 300mcg - 150mcg		0.03	0.023	(-0.01, 0.08)	0.1671
QAB149 300mcg - Formoterol 12mcg		0.04	0.023	(-0.01, 0.08)	0.1024
QAB149 150mcg - Formoterol 12mcg		0.01	0.023	(-0.04, 0.05)	0.8096

Time point: 23 hours 45 min

FEV_1 (L)

Treatment effect / contrast	n	LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	1.47	0.015	(1.44, 1.50)	
QAB149 300mcg	49	1.45	0.016	(1.42, 1.48)	
QAB149 150mcg	47	1.42	0.016	(1.39, 1.45)	
Formoterol 12mcg	50	1.41	0.015	(1.38, 1.44)	
Placebo	48	1.29	0.016	(1.26, 1.32)	
QAB149 600mcg - Placebo		0.18	0.022	(0.14, 0.22)	<.001
QAB149 300mcg - Placebo		0.16	0.022	(0.12, 0.21)	<.001
QAB149 150mcg - Placebo		0.14	0.022	(0.09, 0.18)	<.001
Formoterol 12mcg - Placebo		0.12	0.022	(0.08, 0.16)	<.001
QAB149 600mcg - 300mcg		0.02	0.022	(-0.03, 0.06)	0.4726
QAB149 600mcg - 150mcg		0.04	0.022	(0.00, 0.09)	0.0461
QAB149 600mcg - Formoterol 12mcg		0.06	0.021	(0.02, 0.10)	0.0053
QAB149 300mcg - 150mcg		0.03	0.022	(-0.01, 0.07)	0.1926
QAB149 300mcg - Formoterol 12mcg		0.04	0.022	(0.00, 0.09)	0.0400
QAB149 150mcg - Formoterol 12mcg		0.02	0.022	(-0.03, 0.06)	0.4585

Analysis of covariance of FVC (L) by time point (mITT population)

Time point: 30 min

FVC (L)

Treatment effect / contrast	n	LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	49	3.13	0.027	(3.07, 3.18)	
QAB149 300mcg	49	3.17	0.028	(3.11, 3.22)	
QAB149 150mcg	47	3.15	0.029	(3.09, 3.20)	
Formoterol 12mcg	50	3.13	0.027	(3.08, 3.18)	
Placebo	49	2.81	0.028	(2.76, 2.87)	
QAB149 600mcg - Placebo		0.32	0.039	(0.24, 0.39)	<.001
QAB149 300mcg - Placebo		0.35	0.039	(0.28, 0.43)	<.001
QAB149 150mcg - Placebo		0.33	0.039	(0.26, 0.41)	<.001
Formoterol 12mcg - Placebo		0.32	0.039	(0.24, 0.39)	<.001
QAB149 600mcg - 300mcg		-0.04	0.039	(-0.12, 0.04)	0.3176
QAB149 600mcg - 150mcg		-0.02	0.039	(-0.10, 0.06)	0.6346
QAB149 600mcg - Formoterol 12mcg		0.00	0.039	(-0.08, 0.07)	0.9655
QAB149 300mcg - 150mcg		0.02	0.039	(-0.06, 0.10)	0.6055
QAB149 300mcg - Formoterol 12mcg		0.04	0.039	(-0.04, 0.11)	0.3328
QAB149 150mcg - Formoterol 12mcg		0.02	0.039	(-0.06, 0.09)	0.6625

Time point: 1 hour

FVC (L)

Treatment effect / contrast	n	LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	3.17	0.029	(3.11, 3.23)	
QAB149 300mcg	49	3.18	0.029	(3.12, 3.23)	
QAB149 150mcg	47	3.11	0.030	(3.05, 3.17)	
Formoterol 12mcg	50	3.17	0.029	(3.11, 3.22)	
Placebo	49	2.88	0.030	(2.82, 2.94)	
QAB149 600mcg - Placebo		0.29	0.041	(0.21, 0.37)	<.001
QAB149 300mcg - Placebo		0.30	0.041	(0.21, 0.38)	<.001
QAB149 150mcg - Placebo		0.23	0.041	(0.15, 0.31)	<.001
Formoterol 12mcg - Placebo		0.29	0.041	(0.20, 0.37)	<.001
QAB149 600mcg - 300mcg		-0.01	0.041	(-0.09, 0.07)	0.8478
QAB149 600mcg - 150mcg		0.06	0.042	(-0.03, 0.14)	0.1777
QAB149 600mcg - Formoterol 12mcg		0.00	0.041	(-0.08, 0.08)	0.9604
QAB149 300mcg - 150mcg		0.06	0.041	(-0.02, 0.15)	0.1226
QAB149 300mcg - Formoterol 12mcg		0.01	0.041	(-0.07, 0.09)	0.8083
QAB149 150mcg - Formoterol 12mcg		-0.05	0.042	(-0.14, 0.03)	0.1931

Time point: 2 hours

FVC (L)

Treatment effect / contrast	n	LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	3.27	0.030	(3.21, 3.33)	
QAB149 300mcg	49	3.24	0.031	(3.17, 3.30)	
QAB149 150mcg	47	3.18	0.032	(3.11, 3.24)	
Formoterol 12mcg	50	3.19	0.030	(3.13, 3.25)	
Placebo	49	2.83	0.031	(2.77, 2.89)	
QAB149 600mcg - Placebo		0.44	0.043	(0.36, 0.53)	<.001
QAB149 300mcg - Placebo		0.40	0.043	(0.32, 0.49)	<.001
QAB149 150mcg - Placebo		0.35	0.043	(0.26, 0.43)	<.001
Formoterol 12mcg - Placebo		0.36	0.043	(0.28, 0.45)	<.001
QAB149 600mcg - 300mcg		0.04	0.043	(-0.05, 0.12)	0.3706
QAB149 600mcg - 150mcg		0.10	0.043	(0.01, 0.18)	0.0270
QAB149 600mcg - Formoterol 12mcg		0.08	0.043	(0.00, 0.16)	0.0602
QAB149 300mcg - 150mcg		0.06	0.043	(-0.03, 0.14)	0.1777
QAB149 300mcg - Formoterol 12mcg		0.04	0.043	(-0.04, 0.13)	0.3255
QAB149 150mcg - Formoterol 12mcg		-0.02	0.043	(-0.10, 0.07)	0.7040

Time point: 4 hours

FVC (L)

Treatment effect / contrast	n	LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	3.26	0.030	(3.20, 3.32)	
QAB149 300mcg	49	3.23	0.030	(3.17, 3.29)	
QAB149 150mcg	47	3.13	0.032	(3.06, 3.19)	
Formoterol 12mcg	50	3.17	0.030	(3.12, 3.23)	
Placebo	49	2.86	0.031	(2.80, 2.92)	
QAB149 600mcg - Placebo		0.40	0.043	(0.32, 0.48)	<.001
QAB149 300mcg - Placebo		0.38	0.042	(0.29, 0.46)	<.001
QAB149 150mcg - Placebo		0.27	0.043	(0.18, 0.35)	<.001
Formoterol 12mcg - Placebo		0.32	0.043	(0.23, 0.40)	<.001
QAB149 600mcg - 300mcg		0.02	0.043	(-0.06, 0.11)	0.5830
QAB149 600mcg - 150mcg		0.13	0.043	(0.05, 0.22)	0.0029
QAB149 600mcg - Formoterol 12mcg		0.08	0.042	(0.00, 0.17)	0.0582
QAB149 300mcg - 150mcg		0.11	0.043	(0.02, 0.19)	0.0136
QAB149 300mcg - Formoterol 12mcg		0.06	0.042	(-0.02, 0.14)	0.1662
QAB149 150mcg - Formoterol 12mcg		-0.05	0.043	(-0.13, 0.04)	0.2655

Time point: 23 hours 10 min

Treatment effect / contrast	n	FVC (L) LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	3.05	0.029	(2.99, 3.10)	
QAB149 300mcg	49	3.06	0.029	(3.00, 3.12)	
QAB149 150mcg	47	3.01	0.030	(2.95, 3.07)	
Formoterol 12mcg	50	2.95	0.029	(2.89, 3.00)	
Placebo	48	2.76	0.030	(2.70, 2.82)	
QAB149 600mcg - Placebo		0.29	0.041	(0.21, 0.37)	<.001
QAB149 300mcg - Placebo		0.30	0.041	(0.22, 0.38)	<.001
QAB149 150mcg - Placebo		0.26	0.041	(0.17, 0.34)	<.001
Formoterol 12mcg - Placebo		0.19	0.041	(0.11, 0.27)	<.001
QAB149 600mcg - 300mcg		-0.01	0.041	(-0.09, 0.07)	0.7813
QAB149 600mcg - 150mcg		0.04	0.041	(-0.05, 0.12)	0.3844
QAB149 600mcg - Formoterol 12mcg		0.10	0.040	(0.02, 0.18)	0.0116
QAB149 300mcg - 150mcg		0.05	0.041	(-0.03, 0.13)	0.2507
QAB149 300mcg - Formoterol 12mcg		0.11	0.041	(0.03, 0.19)	0.0052
QAB149 150mcg - Formoterol 12mcg		0.07	0.041	(-0.01, 0.15)	0.1059

Time point: 23 hours 45 min

Treatment effect / contrast	n	FVC (L) LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	3.05	0.029	(3.00, 3.11)	
QAB149 300mcg	49	3.05	0.030	(3.00, 3.11)	
QAB149 150mcg	47	3.02	0.031	(2.96, 3.08)	
Formoterol 12mcg	50	2.97	0.029	(2.91, 3.02)	
Placebo	48	2.78	0.031	(2.72, 2.84)	
QAB149 600mcg - Placebo		0.27	0.042	(0.19, 0.36)	<.001
QAB149 300mcg - Placebo		0.27	0.042	(0.19, 0.36)	<.001
QAB149 150mcg - Placebo		0.23	0.042	(0.15, 0.32)	<.001
Formoterol 12mcg - Placebo		0.18	0.042	(0.10, 0.27)	<.001
QAB149 600mcg - 300mcg		0.00	0.042	(-0.08, 0.08)	0.9997
QAB149 600mcg - 150mcg		0.04	0.042	(-0.05, 0.12)	0.3747
QAB149 600mcg - Formoterol 12mcg		0.09	0.041	(0.01, 0.17)	0.0349
QAB149 300mcg - 150mcg		0.04	0.042	(-0.05, 0.12)	0.3717
QAB149 300mcg - Formoterol 12mcg		0.09	0.041	(0.01, 0.17)	0.0350
QAB149 150mcg - Formoterol 12mcg		0.05	0.042	(-0.03, 0.13)	0.2354

Analysis of covariance of percent change of FEV_1 (%) from baseline at all post-baseline timepoints (mITT population)

Time point: 30 min

Treatment effect / contrast	n	Percent change of FEV_1 (%) from baseline LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	49	14.10	1.075	(11.98, 16.22)	
QAB149 300mcg	49	15.31	1.099	(13.14, 17.47)	
QAB149 150mcg	47	12.51	1.121	(10.30, 14.72)	
Formoterol 12mcg	50	13.50	1.069	(11.39, 15.61)	
Placebo	49	-0.18	1.122	(-2.40, 2.03)	
QAB149 600mcg - Placebo		14.29	1.557	(11.21, 17.36)	<.001
QAB149 300mcg - Placebo		15.49	1.515	(12.50, 18.48)	<.001
QAB149 150mcg - Placebo		12.69	1.539	(9.65, 15.73)	<.001
Formoterol 12mcg - Placebo		13.68	1.542	(10.64, 16.73)	<.001
QAB149 600mcg - 300mcg		-1.20	1.542	(-4.25, 1.84)	0.4359
QAB149 600mcg - 150mcg		1.60	1.556	(-1.47, 4.67)	0.3066
QAB149 600mcg - Formoterol 12mcg		0.60	1.517	(-2.39, 3.60)	0.6924
QAB149 300mcg - 150mcg		2.80	1.533	(-0.22, 5.82)	0.0694
QAB149 300mcg - Formoterol 12mcg		1.81	1.522	(-1.20, 4.81)	0.2372
QAB149 150mcg - Formoterol 12mcg		-0.99	1.538	(-4.03, 2.04)	0.5187

Time point: 1 hour

Percent change of FEV_1 (%) from baseline

Treatment effect / contrast	n	LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	17.02	1.221	(14.61, 19.43)	
QAB149 300mcg	49	17.34	1.263	(14.84, 19.83)	
QAB149 150mcg	47	11.00	1.288	(8.46, 13.55)	
Formoterol 12mcg	50	15.81	1.229	(13.38, 18.23)	
Placebo	49	1.26	1.290	(-1.28, 3.81)	
QAB149 600mcg - Placebo		15.76	1.779	(12.25, 19.27)	<.001
QAB149 300mcg - Placebo		16.07	1.742	(12.64, 19.51)	<.001
QAB149 150mcg - Placebo		9.74	1.770	(6.25, 13.23)	<.001
Formoterol 12mcg - Placebo		14.55	1.773	(11.05, 18.04)	<.001
QAB149 600mcg - 300mcg		-0.32	1.762	(-3.79, 3.16)	0.8582
QAB149 600mcg - 150mcg		6.02	1.779	(2.51, 9.53)	<.001
QAB149 600mcg - Formoterol 12mcg		1.21	1.733	(-2.21, 4.63)	0.4853
QAB149 300mcg - 150mcg		6.33	1.763	(2.85, 9.81)	<.001
QAB149 300mcg - Formoterol 12mcg		1.53	1.751	(-1.93, 4.98)	0.3841
QAB149 150mcg - Formoterol 12mcg		-4.80	1.769	(-8.29, -1.32)	0.0072

Time point: 2 hours

Percent change of FEV_1 (%) from baseline

Treatment effect / contrast	n	LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	19.61	1.148	(17.35, 21.88)	
QAB149 300mcg	49	18.77	1.187	(16.43, 21.11)	
QAB149 150mcg	47	13.51	1.211	(11.13, 15.90)	
Formoterol 12mcg	50	17.81	1.155	(15.53, 20.08)	
Placebo	49	0.08	1.212	(-2.31, 2.47)	
QAB149 600mcg - Placebo		19.54	1.672	(16.24, 22.84)	<.001
QAB149 300mcg - Placebo		18.69	1.637	(15.46, 21.92)	<.001
QAB149 150mcg - Placebo		13.44	1.663	(10.16, 16.72)	<.001
Formoterol 12mcg - Placebo		17.73	1.666	(14.44, 21.02)	<.001
QAB149 600mcg - 300mcg		0.85	1.656	(-2.42, 4.11)	0.6105
QAB149 600mcg - 150mcg		6.10	1.672	(2.80, 9.40)	<.001
QAB149 600mcg - Formoterol 12mcg		1.81	1.629	(-1.41, 5.02)	0.2693
QAB149 300mcg - 150mcg		5.25	1.657	(1.99, 8.52)	0.0019
QAB149 300mcg - Formoterol 12mcg		0.96	1.645	(-2.28, 4.21)	0.5588
QAB149 150mcg - Formoterol 12mcg		-4.29	1.662	(-7.57, -1.01)	0.0106

Time point: 4 hours

Percent change of FEV_1 (%) from baseline

Treatment effect / contrast	n	LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	18.96	1.123	(16.74, 21.17)	
QAB149 300mcg	49	18.66	1.161	(16.37, 20.95)	
QAB149 150mcg	47	12.15	1.184	(9.82, 14.49)	
Formoterol 12mcg	50	15.65	1.130	(13.42, 17.88)	
Placebo	49	-0.02	1.186	(-2.36, 2.32)	
QAB149 600mcg - Placebo		18.97	1.635	(15.75, 22.20)	<.001
QAB149 300mcg - Placebo		18.68	1.601	(15.52, 21.84)	<.001
QAB149 150mcg - Placebo		12.17	1.627	(8.96, 15.38)	<.001
Formoterol 12mcg - Placebo		15.67	1.630	(12.45, 18.88)	<.001
QAB149 600mcg - 300mcg		0.30	1.620	(-2.90, 3.49)	0.8549
QAB149 600mcg - 150mcg		6.80	1.635	(3.58, 10.03)	<.001
QAB149 600mcg - Formoterol 12mcg		3.31	1.593	(0.16, 6.45)	0.0393
QAB149 300mcg - 150mcg		6.51	1.621	(3.31, 9.70)	<.001
QAB149 300mcg - Formoterol 12mcg		3.01	1.609	(-0.16, 6.19)	0.0629
QAB149 150mcg - Formoterol 12mcg		-3.50	1.626	(-6.70, -0.29)	0.0328

Time point: 23 hours 10 min

Treatment effect / contrast	n	Percent change of FEV_1 (%) from baseline LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	9.22	1.159	(6.94, 11.51)	
QAB149 300mcg	49	8.67	1.202	(6.30, 11.04)	
QAB149 150mcg	47	6.80	1.226	(4.38, 9.21)	
Formoterol 12mcg	50	5.01	1.166	(2.71, 7.31)	
Placebo	49	-3.56	1.242	(-6.01, -1.11)	
QAB149 600mcg - Placebo		12.78	1.700	(9.43, 16.14)	<.001
QAB149 300mcg - Placebo		12.23	1.665	(8.94, 15.51)	<.001
QAB149 150mcg - Placebo		10.36	1.686	(7.03, 13.69)	<.001
Formoterol 12mcg - Placebo		8.57	1.692	(5.23, 11.91)	<.001
QAB149 600mcg - 300mcg		0.56	1.673	(-2.75, 3.86)	0.7402
QAB149 600mcg - 150mcg		2.43	1.690	(-0.91, 5.76)	0.1524
QAB149 600mcg - Formoterol 12mcg		4.22	1.646	(0.97, 7.46)	0.0112
QAB149 300mcg - 150mcg		1.87	1.675	(-1.43, 5.18)	0.2649
QAB149 300mcg - Formoterol 12mcg		3.66	1.662	(0.38, 6.94)	0.0289
QAB149 150mcg - Formoterol 12mcg		1.79	1.680	(-1.53, 5.10)	0.2886

Time point: 23 hours 45 min

Treatment effect / contrast	n	Percent change of FEV_1 (%) from baseline LSMean	SE	95% CI	p-value (two-sided)
QAB149 600mcg	50	10.39	1.110	(8.20, 12.58)	
QAB149 300mcg	49	9.30	1.151	(7.03, 11.57)	
QAB149 150mcg	47	7.38	1.174	(5.06, 9.70)	
Formoterol 12mcg	50	5.32	1.117	(3.11, 7.52)	
Placebo	49	-2.45	1.190	(-4.80, -0.11)	
QAB149 600mcg - Placebo		12.85	1.628	(9.63, 16.06)	<.001
QAB149 300mcg - Placebo		11.76	1.594	(8.61, 14.90)	<.001
QAB149 150mcg - Placebo		9.83	1.614	(6.65, 13.02)	<.001
Formoterol 12mcg - Placebo		7.77	1.620	(4.57, 10.97)	<.001
QAB149 600mcg - 300mcg		1.09	1.602	(-2.07, 4.25)	0.4972
QAB149 600mcg - 150mcg		3.01	1.619	(-0.18, 6.21)	0.0644
QAB149 600mcg - Formoterol 12mcg		5.07	1.576	(1.96, 8.18)	0.0015
QAB149 300mcg - 150mcg		1.92	1.604	(-1.24, 5.09)	0.2323
QAB149 300mcg - Formoterol 12mcg		3.98	1.592	(0.84, 7.13)	0.0132
QAB149 150mcg - Formoterol 12mcg		2.06	1.609	(-1.11, 5.24)	0.2014

Analysis of covariance of standardized AUC (30 min-4 h) of FEV_1 (L) (Modified intent-to-treat population)

Treatment effect / contrast	n	Standardized AUC (30 min - 4 h) of FEV_1 LSMean	SE	95% CI	p-value (2-sided)
Indacaterol 600 µg	49	1.56	0.012	(1.54, 1.58)	
Indacaterol 300 µg	49	1.55	0.012	(1.53, 1.58)	
Indacaterol 150 µg	47	1.48	0.012	(1.46, 1.51)	
Formoterol 12 µg	50	1.54	0.012	(1.51, 1.56)	
Placebo	49	1.33	0.012	(1.31, 1.36)	
Indacaterol 600 µg - Placebo		0.23	0.017	(0.20, 0.26)	<.001
Indacaterol 300 µg - Placebo		0.22	0.017	(0.19, 0.26)	<.001
Indacaterol 150 µg - Placebo		0.15	0.017	(0.12, 0.19)	<.001
Formoterol 12 µg - Placebo		0.21	0.017	(0.17, 0.24)	<.001
Indacaterol 600 µg - 300 µg		0.01	0.017	(-0.03, 0.04)	0.6715
Indacaterol 600 µg - 150 µg		0.08	0.017	(0.04, 0.11)	<.001
Indacaterol 600 µg - Formoterol 12 µg		0.02	0.017	(-0.01, 0.06)	0.1350
Indacaterol 300 µg - 150 µg		0.07	0.017	(0.04, 0.10)	<.001

Indacaterol 300 µg - Formoterol 12 µg	0.02	0.017	(-0.02, 0.05)	0.2877
Indacaterol 150 µg - Formoterol 12 µg	-0.05	0.017	(-0.09, -0.02)	0.0018

Safety Results

Adverse events overall and by system organ class (Safety population)

	n (%) patients					
	Indacaterol 150 µg N = 47	**Indacaterol 300 µg N = 49**	**Indacaterol 600 µg N = 51**	**Formoterol 12 µg N = 50**	**Placebo N = 49**	**All indacaterol N = 51**
Total no. of patients with AEs	5 (10.6)	6 (12.2)	3 (5.9)	1 (2.0)	4 (8.2)	10 (19.6)
Primary system organ class affected						
Infections and infestations	3 (6.4)	3 (6.1)	0 (-)	1 (2.0)	2 (4.1)	6 (11.8)
Respiratory, thoracic and mediastinal disorders	3 (6.4)	2 (4.1)	2 (3.9)	0 (-)	3 (6.1)	3 (5.9)
General disorders and administration site conditions	1 (2.1)	1 (2.0)	0 (-)	0 (-)	0 (-)	2 (3.9)
Metabolism and nutrition disorders	0 (-)	1 (2.0)	1 (2.0)	0 (-)	0 (-)	2 (3.9)
Blood and lymphatic system disorders	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Investigations	0 (-)	1 (2.0)	0 (-)	0 (-)	0 (-)	1 (2.0)
Nervous system disorders	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Renal and urinary disorders	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Cardiac disorders	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)	0 (-)
Musculoskeletal and connective tissue disorders	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)	0 (-)

A subject with multiple AEs on one treatment and in one system organ class is only counted once in that organ class and on that treatment, regardless of the number of AEs
Only system organ classes in which AEs were reported are shown

Most Frequently Reported AEs Overall by Preferred Term n (%)

Preferred term	n (%) patients					
	Indacaterol 150 µg N = 47	Indacaterol 300 µg N = 49	Indacaterol 600 µg N = 51	Formoterol 12 µg N = 50	Placebo N = 49	All indacaterol N = 51
Infections and infestations						
Nasopharyngitis	2 (4.3)	2 (4.1)	0 (-)	0 (-)	0 (-)	4 (7.8)
Rhinitis	1 (2.1)	1 (2.0)	0 (-)	0 (-)	1 (2.0)	2 (3.9)
Gastroenteritis	0 (-)	0 (-)	0 (-)	1 (2.0)	1 (2.0)	0 (-)
Sinusitis	0 (-)	0 (-)	0 (-)	1 (2.0)	0 (-)	0 (-)
Respiratory, thoracic and mediastinal disorders						
Cough	3 (6.4)	2 (4.1)	2 (3.9)	0 (-)	1 (2.0)	3 (5.9)
Pharyngolaryngeal pain	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Productive cough	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Chronic obstructive pulmonary disease[1]	0 (-)	0 (-)	0 (-)	1 (2.0)	2 (4.1)	0 (-)
General disorders and administration site conditions						
Chest pain	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Oedema peripheral	0 (-)	1 (2.0)	0 (-)	0 (-)	0 (-)	1 (2.0)
Metabolism and nutrition disorders						
Hypertriglyceridaemia	0 (-)	0 (-)	1 (2.0)	0 (-)	0 (-)	1 (2.0)
Hypoglycaemia	0 (-)	1 (2.0)	0 (-)	0 (-)	0 (-)	1 (2.0)
Blood and lymphatic system disorders						
Neutrophilia	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Investigations						
Blood glucose decreased	0 (-)	1 (2.0)	0 (-)	0 (-)	0 (-)	1 (2.0)
Nervous system disorders						
Somnolence	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Renal and urinary disorders						
Haematuria	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Cardiac disorders						
Myocardial ischaemia	0 (-)	0 (-)	0 (-)	1 (2.0)	0 (-)	0 (-)
Tachycardia	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)	0 (-)
Musculoskeletal and connective tissue disorders						
Back pain	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)	0 (-)

A subject with multiple AEs corresponding to one preferred term on one treatment is only counted once in that preferred term and on that treatment, regardless of the number of AEs

[1]COPD was reported as an AE when the condition worsened from baseline

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or related discontinuations – n (%) of patients (Safety population)

	n (%) patients					
	Indacaterol 150 µg N = 47	Indacaterol 300 µg N = 49	Indacaterol 600 µg N = 51	Formoterol 12 µg N = 50	Placebo N = 49	All indacaterol N=51
Total no. of patients with AEs	5 (10.6)	6 (12.2)	3 (5.9)	1 (2.0)	4 (8.2)	10 (19.6)
Serious or other clinically significant adverse events						
AEs requiring additional therapy	3 (6.4)	2 (4.1)	0 (-)	1 (2.0)	4 (8.2)	5 (9.8)
Discontinuation due to non-serious AEs	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)	0 (-)

Other Relevant Findings

Summary of pharmacokinetic parameters of serum indacaterol after single inhaled doses of 150 µg, 300 µg, and 600 µg

Dose	Statistic	t_{max} [h]	C_{max} [pg/mL]	C_{max}/Dose [pg/mL/µg]	AUC_{0-24} [pg*h/mL]	AUC_{0-24}/Dose [pg*h/mL/µg]
150 µg	Mean	-	145.4	0.97	1284	8.56
(N=47)	SD	-	65.2	0.434	646	4.3
	Min	0.48	23.9	0.159	201	1.34
	Median	0.58	142	0.947	1145	7.63
	Max	1.25	367	2.447	3370	22.47
	CV%	-	44.8	44.8	50.3	50.3
	Geo. Mean	-	131.8	0.879	1140	7.60
300 µg	Mean	-	327.9	1.093	2975	9.92
(N=46)	SD	-	151.4	0.505	1663	5.54
	Min	0.5	35.3	0.118	213	0.71
	Median	0.59	325	1.083	2670	8.9
	Max	4.12	751	2.503	8142	27.14
	CV%	-	46.2	46.2	55.9	55.9
	Geo. Mean	-	287.9	0.96	2406	8.45
600 µg	Mean	-	680.5	1.134	6017	10.03
(N=50)	SD	-	331.7	0.553	3161	5.27
	Min	0.42	213	0.355	1162	1.94
	Median	0.58	610.5	1.018	5550	9.25
	Max	1.15	1730	2.883	18330	30.55
	CV%	-	48.7	48.7	52.5	52.5
	Geo. Mean	-	609.6	1.016	5344	8.91

Vital signs abnormalities (newly occurring or worsened) – n (%) of patients (Safety population)

	Indacaterol 150 µg N=47	Indacaterol 300 µg N=49	Indacaterol 600 µg N=51	Formoterol 12 µg N=50	Placebo N=49	All indacaterol N=51
Pulse rate - worst maximum post-baseline value						
Any abnormality	10 (21.3)	10 (20.4)	14 (27.5)	9 (18.0)	12 (24.5)	16 (31.4)
Above 90 bpm	10 (21.3)	10 (20.4)	14 (27.5)	9 (18.0)	12 (24.5)	16 (31.4)
Systolic blood pressure - worst maximum post-baseline value						
Any abnormality	20 (42.6)	25 (51.0)	24 (47.1)	23 (46.0)	25 (51.0)	30 (58.8)
Above 140 mmHg	20 (42.6)	25 (51.0)	24 (47.1)	23 (46.0)	25 (51.0)	30 (58.8)
Diastolic blood pressure - worst maximum post-baseline value						
Any abnormality	9 (19.1)	13 (26.5)	11 (21.6)	8 (16.0)	15 (30.6)	15 (29.4)
Above 90 mmHg	9 (19.1)	13 (26.5)	11 (21.6)	8 (16.0)	15 (30.6)	15 (29.4)

Any abnormality = Number of patients displaying abnormal values
The limits of the ranges are mutually exclusive
Pulse rate: "Above 90" means min >= 40 and max > 90
Systolic blood pressure: "Above 140" means min >= 90 and max > 140
Diastolic blood pressure: "Above 90" means min >= 50 and max > 90

Overall incidence of abnormal QTc values, change in QTc from baseline and most significant ECG result (Safety population)

	n (%) patients					
	Indacaterol 150 µg N=47	Indacaterol 300 µg N=49	Indacaterol 600 µg N=51	Formoterol 12 µg N=50	Placebo N=49	All indacaterol N=51
Absolute QTc values						
Patients with QTc determination	47	49	51	50	49	51
QTc (Bazett's formula) - maximum post-baseline value						
QTc >450 ms (males)	3 (6.4)	4 (8.2)	4 (7.8)	3 (6.0)	2 (4.1)	6 (11.8)
QTc >470 ms (females)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
Total notable	3 (6.4)	4 (8.2)	4 (7.8)	3 (6.0)	2 (4.1)	6 (11.8)
QTc (Fridericia's formula) - maximum post-baseline value						
QTc >450 ms (males)	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
QTc >470 ms (females)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
Total notable	1 (2.1)	0 (-)	0 (-)	0 (-)	0 (-)	1 (2.0)
Change from baseline in QTc						
Patients with QTc change from baseline calculated	47	49	51	50	49	51
QTc (Bazett's formula) - maximum post-baseline value						

< 30 ms	44 (93.6)	45 (91.8)	49 (96.1)	46 (92.0)	46 (93.9)	43 (84.3)
30-60 ms	3 (6.4)	4 (8.2)	2 (3.9)	4 (8.0)	3 (6.1)	8 (15.7)
> 60 ms	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
QTc (Fridericia's formula) - maximum post-baseline value						
< 30 ms	45 (95.7)	49 (100.0)	49 (96.1)	49 (98.0)	47 (95.9)	48 (94.1)
30-60 ms	2 (4.3)	0 (-)	2 (3.9)	1 (2.0)	2 (4.1)	3 (5.9)
> 60 ms	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
Overall ECG evaluation						
Patients with ECG result	47	49	51	50	49	51
Most Significant ECG Result - post-baseline						
Normal	26 (55.3)	28 (57.1)	30 (58.8)	26 (52.0)	28 (57.1)	24 (47.1)
Abnormal, Clinically insignificant	21 (44.7)	21 (42.9)	21 (41.2)	24 (48.0)	21 (42.9)	27 (52.9)
Abnormal, Clinically significant	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)

Bazett's formula: QTc = QT / square root (RR)
Fridericia's formula: QTc = QT / cube root (RR)

Mean changes from baseline in serum potassium and blood glucose (Safety population)

	Mean (SD) change from baseline (mmol/L)				
	Indacaterol 150 µg N = 47	**Indacaterol 300 µg N = 49**	**Indacaterol 600 µg N = 51**	**Formoterol 12 µg N = 50**	**Placebo N = 49**
Serum potassium					
30 minutes	0.02 (0.349)	0.06 (0.431)	-0.05 (0.357)	-0.05 (0.379)	0.05 (0.340)
1 hour	0 (0.246)	0.04 (0.414)	-0.09 (0.356)	-0.06 (0.399)	0 (0.355)
4 hours	-0.15 (0.386)	-0.19 (0.404)	-0.22 (0.483)	-0.30 (0.405)	-0.17 (0.383)
23 hours 45 minutes	-0.03 (0.382)	0.01 (0.373)	-0.07 (0.397)	-0.08 (0.379)	-0.07 (0.387)
Blood glucose					
30 minutes	-0.24 (0923)	0.16 (0.790)	0.06 (1.256)	0.01 (1.017)	0.10 (1.170)
1 hour	-0.01 (1.253)	0.10 (1.028)	-0.02 (1.231)	-0.05 (1.179)	-0.17 (1.338)
4 hours	0.17 (1.815)	0.20 (1.834)	0.68 (1.943)	1.00 (1.581)	-0.06 (2.089)
23 hours 45 minutes	-0.04 (1.240)	0.21 (1.526)	-0.49 (0.950)	-0.14 (1.198)	-0.54 (1.602)

Date of Clinical Trial Report

Draft report

Date Inclusion on Novartis Clinical Trial Results Database

Jan 2008

Date of Latest Update

Jan 2008