Sponsor

Novartis

Generic Drug Name

Indacaterol

Therapeutic Area of Trial

Chronic obstructive pulmonary disease

Approved Indication

Chronic obstructive pulmonary disease

Study Number

CQAB149B2341

Title

A randomized, double-blind, controlled, parallel group, 12-week treatment study to compare the efficacy and safety of the combination of indacaterol 150 µg once daily with open label tiotropium 18 µg once daily versus open label tiotropium 18 µg once daily in patients with moderate-to severe chronic obstructive pulmonary disease

Phase of Development

Phase IIIb

Study Start/End Dates

05-Mar-2009 to 17-Mar-2010

Study Design/Methodology

A multicenter, multinational, randomized, double-blind, parallel-group study to compare the efficacy and safety of indacaterol 150 µg once-daily (od) plus tiotropium 18 µg od with that of tiotropium 18 µg od alone. Eligible patients were randomized 1:1 to receive treatment for 12 weeks

Centres

There were 186 centers in 14 countries: Argentina (10), Australia (6), Colombia (5), Denmark (5), Germany (25), Greece (4), Guatemala (5), Mexico (5), Peru (6), Philippines (2), South Africa (6), Spain (13), Turkey (13), and USA (81).

Publication

None

Objectives

Primary objective(s)

- Standardized area under the curve (AUC) forced expiratory volume in 1 second (FEV_1) between 5 min – 8 h post-dose after 12 weeks of treatment

Secondary objective(s)

Included:

- Trough FEV_1 24 h post-dose after 12 weeks of treatment
- FEV_1 AUC between 5 min – 8 h post-dose on Day 1
- FEV_1 AUC between 5 min – 4 h post-dose on Day 1
- FEV_1 AUC between 5 min – 4 h post-dose after 12 weeks of treatment
- Trough FEV_1 24 h post-dose after one day of treatment

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

Indacaterol 150 µg, inhaled od via single-dose dry powder inhaler (SDDPI) plus tiotropium 18 µg, inhaled od via SDDPI

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

Tiotropium 18 µg, inhaled od via SDDPI, plus placebo (to indacaterol), inhaled od via SDDPI

Criteria for Evaluation

Primary variables

- FEV_1 AUC between 5 min – 8 h post-dose after 12 weeks of treatment

Secondary variables

Included:

- FEV_1 AUC between 5 min – 8 h post-dose on Day 1
- FEV_1 AUC between 5 min – 4 h post-dose on Day 1 and after 12 weeks of treatment
- Trough FEV_1 24 h post-dose after 1 day and after 12 weeks of treatment

Safety and tolerability

Included monitoring and recording all adverse events and serious adverse events

Statistical Methods

The primary efficacy variable was analyzed by using a mixed model containing treatment as a fixed effect with the baseline FEV_1 measurement, as well as FEV_1 prior to inhalation and FEV_1 10–15 min post-inhalation of salbutamol (components of short-acting β_2-agonist [SABA] reversi-

bility at screening), FEV_1 prior to inhalation and FEV_1 one hour post-inhalation of ipratropium (components of anti-cholinergic reversibility at screening) as covariates. To reflect the randomization scheme the model also included the disease status (moderate/severe), and country as fixed effects with center nested within country as a random effect. In addition, smoking history and inhaled corticosteroid use were included as fixed effects.

Estimates of adjusted treatment effects and estimates of treatment contrasts for the indacaterol 150 µg + tiotropium 18 µg od combination minus tiotropium 18 µg od were displayed along with the associated 95% confidence intervals and their two-sided p-values. Superiority was demonstrated if the two-sided p-value was less than 0.05 and the 95% confidence interval lied entirely to the right of (higher than) 0 mL.

The secondary efficacy variables were analyzed using a similar mixed model.

The safety endpoints were summarized for the safety population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key Inclusion Criteria:

- Diagnosis of COPD (moderate-to-severe as classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines, 2007) and:
    - Smoking history of at least 10 pack-years
    - Post-bronchodilator FEV_1 ≤65% and ≥30% of the predicted normal value
    - Post-bronchodilator FEV_1/FVC (forced vital capacity) <70%

Key Exclusion Criteria:

- Patients who have received systemic corticosteroids and/or antibiotics and/or was hospitalized for a COPD exacerbation in the 6 weeks prior to screening or during the run-in period
- Patients who have had a respiratory tract infection within 6 weeks prior to screening
- Patients with concomitant pulmonary disease
- Patients with a history of asthma
- Patients with diabetes Type I or uncontrolled diabetes Type II
- Any patient with lung cancer or a history of lung cancer
- Patients with a history of certain cardiovascular comorbid conditions

Other protocol-defined inclusion/exclusion criteria may apply

Number of Subjects

	Ind + Tio n (%)	Tio n (%)	Total n (%)
Patients			
Screened	-	-	2136
Randomized	570 (100.0)	564 (100.0)	1134 (100.0)
Exposed	570 (100.0)	561 (99.5)	1131 (99.7)
Completed	531 (93.2)	529 (93.8)	1060 (93.5)
Discontinued	39 (6.8)	35 (6.2)	74 (6.5)
Primary reason for premature discontinuation			
Adverse event(s)	20 (3.5)	10 (1.8)	30 (2.6)
Subject withdrew consent	8 (1.4)	10 (1.8)	18 (1.6)
Administrative problems	5 (0.9)	4 (0.7)	9 (0.8)
Death	2 (0.4)	0 (0.0)	2 (0.2)
Protocol deviation	2 (0.4)	6 (1.1)	8 (0.7)
Abnormal test procedure result(s)	1 (0.2)	0 (0.0)	1 (0.1)
Lost to follow-up	1 (0.2)	4 (0.7)	5 (0.4)
Unsatisfactory therapeutic effect	0 (0.0)	1 (0.2)	1 (0.1)

Demographic Characteristics

		Ind + Tio N = 570	Tio N = 561	Total N = 1131
Age (years)	n	570	561	1131
	Mean	64.0	63.4	63.7
	SD	9.07	9.22	9.14
	Median	64.0	64.0	64.0
	Min - Max	40 - 89	40 - 87	40 - 89
Age group – n (%)	19 – 39 years	0 (0.0)	0 (0.0)	0 (0.0)
	40 – 64 years	292 (51.2)	307 (54.7)	599 (53.0)
	≥ 65 years	278 (48.8)	254 (45.3)	532 (47.0)
Sex – n (%)	Male	399 (70.0)	378 (67.4)	777 (68.7)
	Female	171 (30.0)	183 (32.6)	354 (31.3)
Race – n (%)	Caucasian	446 (78.2)	431 (76.8)	877 (77.5)
	Black	6 (1.1)	17 (3.0)	23 (2.0)
	Asian	31 (5.4)	25 (4.5)	56 (5.0)
	Native American	2 (0.4)	7 (1.2)	9 (0.8)
	Other	85 (14.9)	81 (14.4)	166 (14.7)
Weight (kg)	n	570	561	1131
	Mean	74.3	73.6	74.0
	SD	17.07	16.69	16.88
	Median	74.0	72.0	73.0
	Min - Max	38.0 - 124.3	40.0 - 130.0	38.0 - 130.0
Height (cm)	n	570	561	1131
	Mean	168	168	168
	SD	9.0	9.4	9.2
	Median	168	168	168
	Min - Max	134 -192	136 -191	134 -192
BMI (kg/m²)	n	570	561	1131
	Mean	26.2	26.0	26.1
	SD	5.12	4.89	5.01
	Median	25.9	25.3	25.6
	Min - Max	15.1 - 39.8	15.9 - 39.8	15.1 - 39.8
BMI group – n (%)	≤ 30 kg/m_2	436 (76.5)	452 (80.6)	888 (78.5)
	> 30 kg/m_2	134 (23.5)	109 (19.4)	243 (21.5)

BMI = Body mass index (= weight [kg]/height [m]²)

Primary Objective Result(s)

AUC(5 min–8 h) FEV_1 (L) at Week 12: treatment comparisons

	Treatment			Treatment difference			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Full analysis set								
Ind + Tio	505	1.50	0.014	Ind + Tio - Tio	0.13	0.012	(0.10, 0.15)	< 0.001
Tio	504	1.38	0.014					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: AUC FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + ICS use + COPD severity + country + center(country) + error, with center(country) included as random effect.
* denotes a statistically significant comparison Ind + Tio vs. Tio for the full analysis set only.

Secondary Objective Result(s)

Trough FEV_1 (L) at Week 12: treatment comparisons

	Treatment			Treatment difference			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Full analysis set								
Ind + Tio	561	1.38	0.014	Ind + Tio - Tio	0.08	0.013	(0.05, 0.10)	< 0.001
Tio	549	1.30	0.014					

LOCF = Last observation carried forward, 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 + ICS use + COPD severity + country + center(country) + error, with center(country) included as random effect.
* denotes a statistically significant comparison Ind + Tio vs. Tio for the full analysis set only.

AUC(5min–8h) FEV_1 (L) at Day 1: treatment comparisons

	Treatment			Treatment difference			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Day 1								
Ind + Tio	544	1.40	0.009	Ind + Tio - Tio	0.08	0.008	(0.06, 0.09)	< 0.001
Tio	523	1.32	0.009					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: AUC FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + ICS use + COPD severity + country + center(country) + error, with center(country) included as random effect.

Trough FEV_1 (L) at Day 2: treatment comparisons

	Treatment			Treatment difference			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Day 2								
Ind + Tio	553	1.36	0.011	Ind + Tio - Tio	0.09	0.010	(0.07, 0.11)	< 0.001
Tio	541	1.27	0.012					

LOCF = last observation carried forward, 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 + ICS use + COPD severity + country + center(country) + error, with center(country) included as random effect.

$AUC_{(5min-4h)}$ FEV_1 (L) at Day 1 and Week 12

		Treatment			Treatment difference			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
$AUC_{(5min-4 h)}$ FEV_1 at Day 1								
Ind + Tio	552	1.38	0.008	Ind + Tio - Tio	0.07	0.008	(0.06, 0.09)	<.001
Tio	527	1.31	0.008					
$AUC_{(5min-4 h)}$ FEV_1 at Week 12								
Ind + Tio	516	1.52	0.013	Ind + Tio - Tio	0.14	0.012	(0.11, 0.16)	<.001
Tio	511	1.38	0.013					

Safety Results

Adverse Events by System Organ Class

	Ind + Tio N = 570 n (%)	Tio N = 561 n (%)
Patients with any AE(s)	259 (45.4)	231 (41.2)
Primary system organ class		
Respiratory, thoracic & mediastinal disorders	121 (21.2)	100 (17.8)
Infections & infestations	104 (18.2)	98 (17.5)
Musculoskeletal & connective tissue disorders	41 (7.2)	24 (4.3)
Gastrointestinal disorders	37 (6.5)	42 (7.5)
Nervous system disorders	27 (4.7)	36 (6.4)
Injury, poisoning & procedural complications	17 (3.0)	8 (1.4)
General disorders & administration site conditions	15 (2.6)	16 (2.9)
Cardiac disorders	13 (2.3)	12 (2.1)
Renal & urinary disorders	11 (1.9)	5 (0.9)
Skin & subcutaneous tissue disorders	10 (1.8)	10 (1.8)
Vascular disorders	9 (1.6)	14 (2.5)
Metabolism & nutrition disorders	8 (1.4)	6 (1.1)
Psychiatric disorders	8 (1.4)	5 (0.9)
Eye disorders	6 (1.1)	7 (1.2)
Investigations	4 (0.7)	4 (0.7)
Reproductive system & breast disorders	4 (0.7)	1 (0.2)
Blood & lymphatic system disorders	3 (0.5)	1 (0.2)
Neoplasms benign, malignant & unspecified (incl cysts and polyps)	3 (0.5)	2 (0.4)
Hepatobiliary disorders	2 (0.4)	1 (0.2)
Ear & labyrinth disorders	1 (0.2)	3 (0.5)
Endocrine disorders	1 (0.2)	1 (0.2)
Immune system disorders	1 (0.2)	0 (0.0)

Serious Adverse Events and Deaths

	Ind + Tio N = 570 n (%)	Tio N = 561 n (%)
Patients with any AE(s)	259 (45.4)	231 (41.2)
Serious AEs or AE discontinuations		
Death	2 (0.4)	0 (0.0)
SAE(s)	21 (3.7)	17 (3.0)
Discontinued due to AE(s)	21 (3.7)	9 (1.6)
Discontinued due to SAE(s)	11 (1.9)	3 (0.5)
Discontinued due to non-SAE(s)	10 (1.8)	6 (1.1)

Date of Clinical Trial Report

10 Aug 2010

Date Inclusion on Novartis Clinical Trial Results Database

4 Feb 2011

Date of Latest Update

3 Feb 2011