Sponsor

Novartis

Generic Drug Name

Indacaterol

Therapeutic Area of Trial

Chronic obstructive pulmonary disease

Approved Indication

Chronic obstructive pulmonary disease

Study Number

CQAB149B2351

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

08-Apr-2009 to 09-Feb-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 182 centers in 11 countries: Argentina (9), Canada (16), Colombia (3), Czech Republic (9), Hungary (4), India (9), Netherlands (6), Philippines (3), Slovakia (10), Spain (11) and USA (102).

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	-	-	2075
Randomized	572 (100.0)	570 (100.0)	1142 (100.0)
Exposed	572 (100.0)	570 (100.0)	1142 (100.0)
Completed	543 (94.9)	533 (93.5)	1076 (94.2)
Discontinued	29 (5.1)	37 (6.5)	66 (5.8)
Primary reason for premature discontinuation			
Adverse event(s)	13 (2.3)	14 (2.5)	27 (2.4)
Lost to follow-up	5 (0.9)	3 (0.5)	8 (0.7)
Subject withdrew consent	3 (0.5)	12 (2.1)	15 (1.3)
Subject's condition no longer requires study drug	2 (0.3)	0 (0.0)	2 (0.2)
Administrative problems	2 (0.3)	0 (0.0)	2 (0.2)
Protocol deviation	2 (0.3)	6 (1.1)	8 (0.7)
Unsatisfactory therapeutic effect	1 (0.2)	0 (0.0)	1 (0.1)
Death	1 (0.2)	2 (0.4)	3 (0.3)

Demographic Characteristics

		Ind + Tio N = 572	Tio N = 570	Total N = 1142
Age (years)	n	572	570	1142
	Mean	63.1	62.8	62.9
	SD	8.83	8.98	8.90
	Median	63.0	63.0	63.0
	Min - Max	41 - 86	40 - 89	40 - 89
Age group – n (%)	19 – 39 years	0 (0.0)	0 (0.0)	0 (0.0)
	40 – 64 years	318 (55.6)	314 (55.1)	632 (55.3)
	≥ 65 years	254 (44.4)	256 (44.9)	510 (44.7)
Sex – n (%)	Male	360 (62.9)	387 (67.9)	747 (65.4)
	Female	212 (37.1)	183 (32.1)	395 (34.6)
Race – n (%)	Caucasian	445 (77.8)	452 (79.3)	897 (78.5)
	Black	17 (3.0)	11 (1.9)	28 (2.5)
	Asian	95 (16.6)	94 (16.5)	189 (16.5)
	Other	15 (2.6)	13 (2.3)	28 (2.5)
Weight (kg)	n	572	570	1142
	Mean	72.4	72.1	72.3
	SD	18.35	19.02	18.68
	Median	72.0	70.0	71.0
	Min - Max	33.6 - 129.1	36.0 - 145.0	33.6 - 145.0
Height (cm)	n	572	570	1142
	Mean	167	168	168
	SD	8.8	8.8	8.8
	Median	167	168	167
	Min - Max	143 - 195	144 - 198	143 - 198
BMI (kg/m²)	n	572	570	1142
	Mean	25.7	25.4	25.6
	SD	5.52	5.54	5.53
	Median	25.3	24.9	25.2
	Min - Max	15.2 - 39.6	15.2 - 46.9	15.2 - 46.9
BMI group – n (%)	≤ 30 kg/m²	440 (76.9)	451 (79.1)	891 (78.0)
	> 30 kg/m²	132 (23.1)	119 (20.9)	251 (22.0)

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	530	1.46	0.011	Ind + Tio - Tio	0.12	0.012	(0.09, 0.14)	< 0.001*
Tio	504	1.34	0.011					

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	565	1.34	0.010	Ind + Tio - Tio	0.07	0.011	(0.05, 0.09)	< 0.001*
Tio	564	1.27	0.010					

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	551	1.40	0.007	Ind + Tio - Tio	0.07	0.007	(0.05, 0.08)	<.001
Tio	540	1.33	0.007					

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	563	1.34	0.008	Ind + Tio - Tio	0.08	0.008	(0.06, 0.09)	<.001
Tio	558	1.26	0.008					

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**
$AUC_{(5min–4h)}$ FEV_1 at Day 1								
Ind + Tio	556	1.38	0.007	Ind + Tio - Tio	0.06	0.007	(0.05, 0.07)	<.001
Tio	550	1.32	0.007					
$AUC_{(5min–4h)}$ FEV_1 at Week 12								
Ind + Tio	532	1.48	0.011	Ind + Tio - Tio	0.12	0.012	(0.10, 0.15)	<.001
Tio	511	1.35	0.011					

Safety Results

Adverse Events by System Organ Class

	Ind + Tio N = 572 n (%)	Tio N = 570 n (%)
Patients with any AE(s)	246 (43.0)	229 (40.2)
Primary system organ class		
Respiratory, thoracic & mediastinal disorders	115 (20.1)	98 (17.2)
Infections & infestations	87 (15.2)	87 (15.3)
Gastrointestinal disorders	37 (6.5)	22 (3.9)
Nervous system disorders	22 (3.8)	24 (4.2)
General disorders & administration site conditions	19 (3.3)	25 (4.4)
Injury, poisoning & procedural complications	19 (3.3)	12 (2.1)
Musculoskeletal & connective tissue disorders	17 (3.0)	34 (6.0)
Metabolism & nutrition disorders	16 (2.8)	11 (1.9)
Skin & subcutaneous tissue disorders	11 (1.9)	11 (1.9)
Vascular disorders	10 (1.7)	13 (2.3)
Blood & lymphatic system disorders	9 (1.6)	3 (0.5)
Cardiac disorders	9 (1.6)	12 (2.1)
Investigations	9 (1.6)	9 (1.6)
Psychiatric disorders	8 (1.4)	2 (0.4)
Ear & labyrinth disorders	5 (0.9)	2 (0.4)
Eye disorders	5 (0.9)	6 (1.1)
Renal & urinary disorders	4 (0.7)	10 (1.8)
Immune system disorders	3 (0.5)	6 (1.1)
Neoplasms benign, malignant & unspecified (incl cysts and polyps)	3 (0.5)	3 (0.5)
Hepatobiliary disorders	1 (0.2)	1 (0.2)
Endocrine disorders	0 (0.0)	1 (0.2)
Reproductive system & breast disorders	0 (0.0)	5 (0.9)
Social circumstances	0 (0.0)	1 (0.2)

Serious Adverse Events and Deaths

	Ind + Tio N = 572 n (%)	Tio N = 570 n (%)
Patients with any AE(s)	246 (43.0)	229 (40.2)
Serious AEs or AE discontinuations		
Death	1 (0.2)	2 (0.4)
SAE(s)	19 (3.3)	18 (3.2)
Discontinued due to AE(s)	14 (2.4)	16 (2.8)
Discontinued due to SAE(s)	8 (1.4)	8 (1.4)
Discontinued due to non-SAE(s)	6 (1.0)	8 (1.4)

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

Date of Clinical Trial Report

26 July 2010

Date Inclusion on Novartis Clinical Trial Results Database

4 Feb 2011

Date of Latest Update

7 Jan 2011