Sponsor

Novartis

Generic drug name

Indacaterol

Trial indication(s)

Chronic Obstructive Pulmonary Disease (COPD)

Protocol number

CQAB149B2211

Protocol title

An exploratory, double-blind comparison of inspiratory capacity (IC) and FEV1 in COPD patients following single dose administration of indacaterol and placebo and open label b.i.d. administration of formoterol

Clinical trial phase

Phase II

Study Start/End Dates

15-Sep-2006 to 27-Oct-2006

Study Design/Methodology

This study was a multi-center, double-blind, placebo-controlled, randomized crossover study in COPD patients comparing single doses of indacaterol and matching placebo , with an open label arm of a one day treatment with formoterol b.i.d.

Centers

The study was conducted at 3 centers in 3 countries: Germany (1); United Kingdom (1); and Denmark (1).

Objectives:

Primary objective(s)

Comparison of responsiveness and variability of Mean Maximal Change in percent predicted FEV1 from baseline with Mean Maximal Change in IC from baseline following single doses of indacaterol and matched indacaterol placebo with two doses (b.i.d. regimen) of formoterol as an active control.

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

Indacaterol 300 µg delivered via a single dose dry powder inhaler (SDDPI)

Reference therapy, Dose and Mode of Administration

Placebo to indacaterol via SDDPI. Placebo to formoterol via Aerolizer™.

Statistical Methods

All randomized and treated patients who had at least one post-baseline assessment of the efficacy variables (IC or FEV1) were included in the appropriate efficacy analysis.
For all spirometry parameters listed above, the changes from the pre-dose value were computed for each patient at each time point. With these changes from the pre-dose values, the following derived metrics were calculated:

- Peak (E_{max}) after each dose level. This is the maximum effect between 0 and 6 hours after dose
- Time to peak (tmax): this is the time at which Emax occurs the first time

The comparison of E_{max} of FEV1 between indacaterol and placebo was conducted using a mixed linear model with period and treatment (indacaterol, placebo) as fixed effects and subject as a random effect. Trough FEV1 data was compared between indacaterol and placebo using a similar analysis.

The comparison between formoterol versus placebo and between formoterol versus indacaterol were performed using a t-test on E_{max}. This approach assumes that there is no overall period effect that would impact values reported on period 3. It is not possible to distinguish between period effect and treatment effect, since formoterol was only given in period 3. The same approach was used for E_{max} of IC.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Male and post-menopausal female adults aged 40-80 years inclusive.
- Patients with a clinical diagnosis of COPD according to the Global Initiative for Chronic Lung Disease (GOLD) Guidelines (2005)
- Smoking history of at least 10 pack years (i.e. smokers or ex-smokers).
- Able to perform reproducible spirometry maneuvers.
- Able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent.

Exclusion criteria

- COPD exacerbations within 6 weeks prior to dosing
- Concomitant lung disease such as asthma, requirement for long term oxygen treatment or history of lung reduction surgery.
- Medical conditions that would interfere with the performance of spirometry or may pose a potential hazard from performing spirometry.
- Any other medical condition that in the opinion of the Investigator may cause the patient to be unsuitable for completion of the study or place the patient at potential risk from being in the study, e.g. uncontrolled hypertension, unstable ischemic heart disease.
- Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulations, and for any other limitation of participation based on local regulations.

Other protocol-defined inclusion/exclusion criteria may apply

Patient Flow Table

Disposition of patients

	Total n (%)
Started	30 (100.0)
Completed	30 (100.0)

Baseline Characteristics

Demographic summary

		Total (N=30)
Age (years)	Mean	64.8
	Range	51-78
Sex	Male (%)	16 (53.3 %)
	Female (%)	14 (46.7 %)
Race – n (%)	Caucasian	30 (100.0 %)
Weight (kg)	Mean	76.8
	SD	15.95
Height (cm)	Mean	170.7
	SD	6.53

Summary of Efficacy

Primary Outcome Result(s):

Comparison of indacaterol to Placebo for FEV1 E_{max}, Trough FEV1 and IC E_{max} (absolute values)

Variable	Treatment	N	Estimated geometric mean (1)	Ratio to Placebo	95% Confidence Interval	P value
FEV_1 (L)	Placebo	30	1.304			
E_{max}	Indacaterol	30	1.554	1.19	(1.15, 1.23)	<0.001
Trough FEV_1	Placebo	28	1.209			
FEV_1	Indacaterol	28	1.327	1.10	(1.05, 1.14)	<0.001
IC (L)	Placebo	30	2.044			
E_{max}	Indacaterol	30	2.424	1.19	(1.13, 1.24)	<0.001

Emax is the maximum effect observed within up to 6 hours after dose.
A ratio greater than 1 indicates higher values for indacaterol
(1) Back transformed from log scale

Comparison for FEV1, Trough FEV1 and IC Emax expressed as % increase vs. pre-dose

Variable	Treatment	N	Arithmetic mean	95% confidence interval	Comparison to placebo	(t-test P value to Formoterol)
FEV_1 E_{max}	Placebo	30	7.946	(5.49, 10.40)		
	Indacaterol	30	32.323	(26.35, 38.30)	<0.001	0.12
	Formoterol	30	27.864	(23.59, 32.14)	<0.001	
Trough FEV_1	Placebo	28	-2.317	(-5.41, 0.77)		
	Indacaterol	28	14.955	(9.28, 20.63)	<0.001	0.006
	Formoterol	30	6.717	(2.25, 11.18)	<0.001	
IC E_{max}	Placebo	30	8.822	(5.31, 12.34)		
	Indacaterol	30	31.203	(23.72, 38.69)	<0.001	0.034
	Formoterol	30	22.909	(18.17, 27.65)	<0.001	

Summary of Safety

Safety Results

Adverse events overall and frequently affected system organ classes - n (%) of patients (all patients)

	Indacaterol N = 30 n (%)	Placebo N = 30 n (%)	Formoterol N = 30 n (%)
Patients with AE(s)	11 (36.7%)	4 (13.3%)	1 (3.3%)
System organ class			
General disorders and administration site conditions	1 (3.3)	1 (3.3)	
Infections and Infestations		1 (3.3)	
Musculoskeletal and connective tissue disorders	2 (6.7)	1 (3.3)	1 (3.3)
Nervous system disorders			1 (3.3)
Respiratory, thoracic and mediastinal disorders	9 (30.0)	3 (10.0)	

A subject with multiple occurrences of an adverse event is counted only once in the AE category.
A subject with multiple adverse events within a body system is counted only once in the total row.
N = number of subjects studied n = number of subjects with at least one AE in the category

Adverse events overall and most frequent events - n (%) of patients (all patients)

	Indacaterol N = 30 n (%)	Placebo N = 30 n (%)	Formoterol N = 30 n (%)
Patients with AE(s)	11 (36.7%)	4 (13.3%)	1 (3.3%)
Preferred term			
Chest discomfort	1 (3.3)	1 (3.3)	
Nasopharyngitis		1 (3.3)	
Back pain	1 (3.3)	1 (3.3)	1 (3.3)
Myalgia	1 (3.3)		
Headache			1 (3.3)
Cough	6 (20.0)	1 (3.3)	
Dry throat	1 (3.3)		
Dyspnoea	2 (6.7)	2 (6.7)	

A subject with multiple occurrences of an adverse event is counted only once in the AE category.
N = number of subjects studied
n = number of subjects with at least one AE in the category

Serious and other Adverse Events

- No death occurred in this study.
- No SAE event occurred in this study.
- No premature discontinuation due to AE occurred in this study

Other Relevant Findings

None

Date of Clinical Trial Report

13-Oct-2008