Sponsor

Novartis

Generic Drug Name

Indacaterol (QAB149)

Therapeutic Area of Trial

Chronic obstructive pulmonary disease

Approved Indication

Investigational

Study Number

CQAB149B2318

Title

An exploratory, double-blind, randomized, placebo-controlled, 2-way cross-over study to assess the effect of repeat-dose inhaled indacaterol maleate (300 µg) on dynamic and static lung hyper-inflation, subjective breathlessness and health status in patients with COPD

Phase of Development

III

Study Start/End Dates

28 Feb 2008 first patient screened, 05 Aug 2008 last patient completed

Study Design/Methodology

This was a multi-centre, double-blind, randomized, placebo-controlled, 2-way crossover study in 27 patients with a documented diagnosis of mild, moderate or severe COPD, >20-pack year history of smoking and a functional residual capacity of >120% predicted. Patients were randomized to one of two treatment sequences and therefore received both indacaterol 300µg and matched placebo for 14 days in the two different periods.

Centres

4 centres in Germany

Publication

None

Objectives

Primary objective(s)

- To evaluate the effect of 2 weeks treatment with inhaled indacaterol (300 µg) on isotime and peak exercise IC in patients with COPD

Secondary objective(s)

- To evaluate the effect of a single dose treatment with inhaled indacaterol (300 µg) on isotime and peak exercise IC in patients with COPD
- To evaluate the effect of 2 weeks treatment with inhaled indacaterol (300 µg) on static (resting) IC in patients with COPD
- To evaluate the effect of 2 weeks treatment with inhaled indacaterol (300 µg) on trough bronchodilatory efficacy FEV_1 in patients with COPD
- To evaluate the effect of 2 weeks treatment with inhaled indacaterol (300 µg) on chronic activity-related breathlessness (baseline and transition dyspnoea indices) in patients with COPD compared to placebo

To evaluate the effect of 2 weeks treatment with inhaled indacaterol (300 µg) on dyspnoea (during submaximal exercise, measured with the Borg CR10 Scale®) in patients with COPD compared to placebo

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

300µg indacaterol maleate inhalation powder in hard gelatin capsules administered via Concept1 inhalation device

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

Matching placebo devices and hard gelatin capsules

Criteria for Evaluation

Primary variables

- Inspiratory Capacity (IC), at isotime and peak, measured during sub-maximal exercise on Day 14

Secondary variables

- Inspiratory Capacity (IC), at isotime and peak, measured during sub-maximal exercise on Day 1
- Inspiratory Capacity (IC) at rest as measured using whole body plethysmography on Day 14
- Trough FEV_1 measured by spirometryon Day 14
- Dyspnoea measured at baseline using the baseline dyspnoea index (BDI) and during the treatment period using the transition dyspnoea index (TDI) on Day 14
- Dyspnoea during sub-maximal exercise measured with the Borg CR10 Scale® on Day 14

Safety and tolerability

- Collecting all adverse events (AEs) and serious adverse events (SAEs)
- Blood samples for laboratory data (hematology, blood chemistry and urinalysis)
- Vital signs and ECG monitoring
- Continuous ECG monitoring during each exercise test

Pharmacology

None

Statistical Methods

All data collected in this study are listed by sequence and subject. In addition, demographic data, spirometry data, Borg CR10 scale, dyspnoea indices and safety data were summarized using n, mean, SD, median and range or frequency tables as appropriate to the data.
Analysis of covariance was used to compare IC between treatments on day 1 and on day 14 using models that included period, sequence and treatment as fixed effects, patients as random effect and an appropriate baseline measure as covariate. These analyses were summarized by estimates of the adjusted means with associated 90% confidence intervals, and also the estimated difference between indacaterol and placebo with associated 90% CIs and p-values related to this difference. The raw IC data was also summarized split by day and treatment using n, mean, SD, median and range.
Other secondary endpoints (trough FEV_1, Borg CR10, and TDI) were analyzed using similar methods.
No interim analysis was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

1. Male or female (see exclusion criteria 8 below) patients with COPD, aged 40-80 years, with a smoking history of at least 20 pack years (i.e. smokers or ex-smokers).
2. Prior to administration of any study procedures, all subjects must understand and provide written informed consent. Patients must be able to communicate well with the investigator, to understand and comply with the requirements of the study
3. Diagnosis of COPD according to GOLD criteria
4. Body mass index (BMI) must be within the range of 18 to 32 kg/m^2. Patients must weigh at least 50 kg to participate in this study.
5. Post-bronchodilator* 40% = FEV1 at screening = 80% of the predicted normal value
6. Post-bronchodilator* FEV1/FVC < 70%
7. Increase in FEV1 from Pre-bronchodilator to Post-bronchodilator assessment of at least 5%
8. Demonstrated plethysmographic functional residual capacity > 120% predicted normal
9. No history of concomitant lung disease such as asthma, carcinoma, active TB or prior thoracic surgery. No requirement for long term oxygen treatment or history of lung reduction surgery. No medical conditions that would interfere with the performance of spirometry or cardiopulmonary exercise testing. Serum CPK levels must be in the normal range as measured by point-of-care or lab assay at screening and prior to all protocol specified exercise testing.
10. Male patients must be using a double-barrier local contraception, i.e., spermicidal gel plus condom, for the entire duration of the study, up to Study Completion visit, and refrain from fathering a child in the three (3) months following last study drug administration.
11. Women of child-bearing potential; defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL **or** are using one or more of the following acceptable methods of contraception.
    - surgical sterilization (e.g. bilateral tubal ligation, hysterectomy)
    - hormonal contraception (implantable, patch, oral)
    - double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap)
    - Acceptable methods of contraception may include total abstinence at the discretion of the investigator in cases where the age, career, lifestyle, or sexual orientation of the patient ensures compliance. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception. Reliable contraception should be maintained throughout the study and for 30 days after study drug discontinuation

* Post refers to 30 minutes after the inhalation of 400 µg of salbutamol.

The salbutamol must be administered after the subjects have adhered to the following wash-out periods:

- 6h for short-acting bronchodilators
- 48h for long-acting beta-2-agonists
- 3 days for tiotropium

Exclusion criteria:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum human chorionic gonadotrophin laboratory test (> 5 mIU/mL)
2. Patients who have been hospitalized for a COPD exacerbation in the 6 weeks prior to Visit 2 or during the run-in period
3. Patients requiring oxygen therapy or who experience oxygen desaturation to <80% during cycle exercise on room air according to the methodology used by the investigator and in the opinion of the investigator should not participate in the study.
4. Patients who have had a respiratory tract infection within 6 weeks prior to Visit 2. Patients who develop a respiratory tract infection prior to randomization must discontinue from the trial, but may be permitted to re-enroll at a later date (at least 6 weeks after the end of the respiratory tract infection)
5. Patients with contra-indications of cardiopulmonary exercise testing:
    - Acute myocardial infarction (6 months)
    - Unstable angina
    - Uncontrolled arrhythmias causing symptoms or haemodynamic compromise
    - Active endocarditis
    - Acute myocarditis or pericarditis
    - Symptomatic severe aortic stenosis
    - Uncontrolled cardiac failure (NYHA class III / IV)
    - Acute pulmonary embolus or pulmonary infarction
    - Acute noncardiac disorder that may affect exercise performance or be aggravated by exercise (e.g. infection, renal failure, thyrotoxicosis)
    - Left main coronary stenosis or its equivalent
    - Moderate stenotic valvular cardiac disease
    - Clinically Signifigant Electrolyte abnormalities
    - Severe untreated arterial hypertension (>200 mmHg systolic, >120 mmHg diastolic)
    - Siginificant pulmonary hypertension (>30 mmHg mean pulmonary artery pressure)
    - Tachyarrhythmias or bradyarrhythmias
    - Hypertrophic cardiomyopathy
    - Mental impairment leading to inability to cooperate
    - High degree of atrioventricular block (2^{nd} or 3^{rd} Degree)

- Ongoing/ Active thrombosis of lower extremities

6. Patients with significant (investigator evaluation) concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active) or clinically significant bronchiectasis
7. Patients with a history of asthma indicated
8. Women of child-bearing potential; defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, **UNLESS** they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL **OR** are using one or more of the following acceptable methods of contraception.
   - surgical sterilization (e.g. bilateral tubal ligation, hysterectomy)
   - hormonal contraception (implantable, patch, oral)
   - double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap)
   - Acceptable methods of contraception may include total abstinence at the discretion of the investigator in cases where the age, career, lifestyle, or sexual orientation of the patient ensures compliance. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception. Reliable contraception should be maintained throughout the study and for 30 days after study drug discontinuation
9. Patients who, in the judgment of the investigator, have a clinically relevant laboratory abnormality or a clinically significant condition such as (but not limited to) unstable ischemic heart disease, arrhythmia (excluding stable AF), uncontrolled hypertension, uncontrolled hypo- and hyperthyroidism, hypokalemia, hyperadrenergic state or any condition which in the investigator's opinion might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study
10. Any patient with lung cancer or a history of lung cancer
11. Any patient with active cancer or a history of cancer with less than 5 years disease free survival time (whether or not there is evidence of local recurrence or metastases). Localized basal cell carcinoma (without metastases) of the skin is acceptable. Patients with a history of cancer (excluding lung cancer) and 5 years or more disease free survival time may be included in the study at the investigator's discretion on a case-by-case basis
12. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
13. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
14. Patients with a history of long QT syndrome or whose QTc interval (Bazett's) measured at Screening or Visit 4 is prolonged: > 430 ms (males) or > 450 ms (females) as assessed by the investigator. Patients who fail the screening ECG (with the exception of machine failures) should not be re-screened.
15. Patients with a history of hypersensitivity to any of the study drugs or to drugs with similar chemical structures including untoward reactions to sympathomimetic amines or inhaled

medication or any component thereof

16. Patients who have had treatment with investigational drugs at the time of enrollment, or within 30 days or 5 half-lives prior to screening.
17. Treatments for COPD and allied conditions: the following medications must not be used prior to screening for at least the minimum washout period specified below or at any time during the study:
    - The long acting anti-cholinergic agent tiotropium: 3 days
    - Short acting anti-cholinergics: 8 h
    - Fixed combinations of β2-agonists and inhaled corticosteroids: 48 h

      (Patients taking fixed dose combination therapy must be switched to an equivalent inhaled corticosteroid monotherapy plus salbutamol/albuterol as rescue therapy during study participation)
    - Fixed combinations of SABAs plus inhaled anticholinergics: 8 h
    - LABAs: 48 h
    - SABAs (other than those prescribed in the study): 6 h
    - Theophylline and other xanthines: 1 week
    - Parenteral or oral corticosteroids: 1 month
18. Treatments for COPD and allied conditions: The following medications should not be used unless they have been stabilized:
    - Cromoglycate, nedocromil, ketotifen, inhaled or nasal corticosteroids and leukotriene antagonists - at least one month prior to Visit 2
    - Antihistamines (excluding those in 22 below) - at least 5 days prior to Visit 2
19. Other excluded medications:
    - Non-potassium sparing diuretics (unless administered as a fixed dose combination with a potassium conserving drug)
    - Non-selective beta-blocking agents
    - Cardiac anti-arrhythmics Class Ia (e.g., disopyramide, procainamide, quinidine), Class III (e.g., amiodarone, dofetilide, ibutilide, sotalol), terfenadine, astemizole, mizolastin and any other drug with potential to significantly prolong the QT interval.
    - Tricyclic antidepressants and monoamino-oxidase inhibitors. [Fluoxetine or any other selective serotonin uptake receptor inhibitor may only be permitted if the patient's treatment regimen has been stable for at least 1 month prior to Visit 2, their Visit 2 ECG is normal and they have no clinical evidence of prior ECG abnormalities]
20. Patients unable to successfully use a dry powder inhaler device or perform spirometry measurements
21. Patients who experience a decline of PEFR > 15% over one day, or a decline in PEFR > 10% over 3 consecutive days, or have excessive use of their rescue medication > 200mcg qid for 2 consecutive days will be withdrawn from the study.

Number of Subjects

	Total
Patients	
Randomized	27 (100.0)
Completed	24 (88.9)
Discontinued	3 (11.1)
Main cause of discontinuation	
Death	0
Adverse event(s)	1 (3.7)
Lack of efficacy	0
Protocol violation(s)	0
Administrative reasons	2 (7.4)
Other	0

Demographic and Background Characteristics

Variable		Sequence A N=14	Sequence B N=13	Total N=27
Age (years)	Mean(SD)	62.6 (8.30)	59.8 (5.81)	61.3 (7.22)
Height (cm)	Mean(SD)	173.7 (8.14)	170.2 (6.07)	172.0 (7.31)
Weight (kg)	Mean(SD)	78.32 (12.041)	73.42 (13.603)	75.96 (12.811)
BMI (kg/m2)	Mean(SD)	25.87 (3.051)	25.24 (3.769)	25.57 (3.363)
Sex	Female	4 (28.6 %)	5 (38.5 %)	9 (33.3 %)
	Male	10 (71.4 %)	8 (61.5 %)	18 (66.7 %)
Race	Caucasian	14 (100.0 %)	13 (100.0 %)	27 (100.0 %)

Sequence A: Indacaterol (300µg)/Placebo; Sequence B: Placebo/ Indacaterol (300µg)

Primary Objective Result(s)

Summary of statistical analysis of IC on day 14

Treatment	Least squares mean (90% CI)	Contrast to Placebo Least squares mean (90% CI)	P-value
IC at Peak(L)			
Placebo	2.05 (1.93, 2.16)		
Indacaterol 300 µg	2.36 (2.25, 2.48)	0.317 (0.152, 0.483)	0.0033
IC at Isotime(L)			
Placebo	2.10 (1.99, 2.21)		
Indacaterol 300 µg	2.37 (2.25, 2.48)	0.268 (0.132, 0.404)	0.0026

Both peak and isotime IC improved by more than 200 mL over placebo on day 14 (317 mL for peak and 268 mL for isotime). A smaller improvement was found on day 1 following a single dose of study drug, with an increase of 250 mL for peak and an increase of 148 mL for isotime. All these results were statistically significant (P<0.03).

A sequence effect was observed in the analysis of IC at peak time. Within each sequence the raw mean of the treatment difference were 222 mL for sequence A and 404 mL for sequence B. The main result of a treatment difference of 317 mL between the treatments must be interpreted carefully as the data indicates that the treatment difference is different in the two treatment sequences.

Summary statistics of IC on day 14 by sequence and period

			Period 1		Period 2	
Sequence		Baseline*	Day 14	Change from baseline	Day 14	Change from baseline
IC at Isotime (L)						
A: indacaterol/ placebo	n	13	13	13	12	12
	mean	2.451	2.529	0.078	2.231	-0.116
	SD	0.8400	0.8054	0.2116	0.9810	0.4887
B: placebo/ indacaterol	n	13	13	13	12	12
	mean	1.877	1.930	0.053	2.250	0.372
	SD	0.6283	0.5136	0.2775	0.5386	0.2970
IC at Peak (L)						
A: indacaterol/ placebo	n	13	13	13	12	12
	mean	2.460	2.507	0.048	2.183	-0.174
	SD	0.8167	0.7988	0.2905	0.9483	0.4566
B: placebo/ indacaterol	n	13	13	13	12	12
	mean	1.860	1.863	0.003	2.266	0.407
	SD	0.6453	0.5234	0.2599	0.6561	0.3376

*) Baseline is the day -2 profile (for subjects with period 1 day 14 IC)

Secondary Objective Result(s)

Trough FEV_1 data on Day 14, taken as the average of the 23.5 and 24 hour readings, were statistically analyzed as follows:

Summary of the statistical analysis of FEV_1 on day 14

Treatment	Least squares mean (90% CI)	Contrast to Placebo Least squares mean (90% CI)	P-value
Trough FEV1 (L)			
Placebo	1.53 (1.45, 1.62)		
Indacaterol 300 µg	1.68 (1.60, 1.76)	0.145 (0.060, 0.229)	0.0076

Trough FEV_1 on Day 14 for indacaterol was 145 mL better than that for placebo which is a clinically significant improvement over placebo (P=0.0077). Trough FVC on Day 14 also showed an improvement over placebo of 273 mL (90%CI 159 to 388 mL; P<0.001). Given that both of these variables showed similar improvements the FEV_1/FVC ratio changed very little with values of 0.473 for placebo and 0.468 for indacaterol (P=0.99). The raw data indicate that these differences between indacaterol and placebo in trough FEV_1 and trough FVC were also observed after a single dose on day 1.

Whole body plethysmography was used to obtain the resting IC, functional residual capacity, total lung capacity and residual volume post-dose on Days 1 and 14. Resting IC on Day 14 was analyzed and an improvement of 182 mL (90%CI: 70 to 294 mL; P=0.0105) was seen between indacaterol and placebo.

The Borg CR 10 scale score was recorded at isotime and at peak time on both Days 1 and 14. Little difference was seen between indacaterol and placebo on day 1, but a decrease of -1.5 (90%CI: -2.3 to -0.7; P=0.0052) between indacaterol and placebo was seen at isotime on Day 14. A smaller decrease of -0.6 (90%CI: -1.3 to 0.1; P=0.15) was seen at peak time on Day 14. A reduction in this score indicates an improvement.

The baseline dyspnoea index was measured on Day 1 in each treatment period so that there was a BDI for both treatments given to each patient. The mean BDI was very similar at 6.7 and 7.1 for both treatment groups. The transition dyspnoea index was measured on Day 14 of each treatment period. The summary of the statistical analysis of TDI is shown in the table below.

Summary of the statistical analysis of the transition dyspnoea index (TDI) on day 14

Treatment	Least squares mean (90% CI)	Contrast to Placebo Least squares mean (90% CI)	P-value
TDI			
Placebo	-2.3 (-3.6, -1.0)		
Indacaterol 300 µg	0.9 (-0.3, 2.4)	3.33 (1.46, 5.19)	0.0047

The TDI was reduced for placebo and increased for indacaterol resulting in a 3.33 improvement for indacaterol over placebo (P=0.0047).

Safety Results

Multiple inhaled doses of indacaterol 300 µg were well tolerated by patients with COPD. There were no serious adverse events. Most of the AEs reported in the study were mild and moderate in severity. Abnormal clinical laboratory tests reported could not be attributed to any treatment. There were no clinically relevant changes in vital signs and no clinically significant abnormalities were reported. There was one discontinuation due to an adverse event for a patient receiving placebo at the time of discontinuation.

Adverse Events by System Organ Class

System Organ Class	Preferred term	Indacaterol 300µg N = 26 n (%)	Placebo N = 26 n (%)
Any body system	All	9 (35%)	9 (35%)
Gastrointestinal disorders	TOTAL	1 (4%)	3 (12%)
	Abdominal pain	0	1 (4%)
	Constipation	0	1 (4%)
	Diarrhoea	1 (4%)	1 (4%)
	Dry mouth	0	1 (4%)
	Tongue coated	0	1 (4%)
Infections and infestations	Nasopharyngitis	2 (8%)	0
Investigations	TOTAL	0	2 (8%)
	BP increased	0	1 (4%)
	ECG ST segment depression	0	1 (4%)
Musculoskeletal and connective tissue disorders	TOTAL	0	3 (12%)
	Back pain	0	2 (8%)
	Osteitis	0	1 (4%)
	Pain in jaw	0	1 (4%)
Nervous system disorders	Headache	3 (12%)	1 (4%)
Respiratory, thoracic and mediastinal disorders	Cough	2 (8%)	0

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

See table above

Serious Adverse Events and Deaths

No serious adverse events or deaths were reported.

Other Relevant Findings

None

Date of Clinical Trial Report

5 November 2008

Date Inclusion on Novartis Clinical Trial Results Database

04-August-2009

Date of Latest Update

31st July 2009