Sponsor

Novartis

Generic Drug Name

Indacaterol maleate

Therapeutic Area of Trial

Mild to moderate persistent asthma

Approved Indication

Approved for the once-daily maintenance treatment of airflow obstruction in patients with moderate to severe COPD (applies to EEA)

Study Number

CQAB149B2102

Title

A multi-center, randomized, single-dose, double-blind, 4-way cross over study to evaluate tolerability following treatment with indacaterol salts (maleate, xinafoate and acetate) in comparison to placebo in patients with mild to moderate persistent asthma

Phase of Development

Phase II

Study Start/End Dates

14 Feb 2008 to 23 Sep 2008

Study Design/Methodology

This was a multi-center, randomized, single-dose, double-blind, 4-way cross-over study. Ninety-eight (98) patients with mild to moderate persistent asthma were enrolled. Each subject participated in a 21-day screening period, four baseline periods (one prior to each treatment period), 4 treatment periods and a study completion evaluation after the last drug administration.

Eligibility was confirmed on the morning of each treatment period. All baseline safety evaluation results were available prior to dosing. Patients who satisfied all inclusion criteria on the morning of treatment period 1 were randomized to one of four treatment sequences as determined by a computer-generated randomization schedule provided by the sponsor.

Treatment sequences

Sequence	Period 1	Period 2	Period 3	Period 4
I	A	D	B	C
II	B	A	C	D
III	C	B	D	A
IV	D	C	A	B

- Treatment A Indacaterol maleate 400 µg via SDDPI (single dose)
- Treatment B Indacaterol xinafoate 400 µg via SDDPI (single dose)
- Treatment C Indacaterol acetate 400 µg via SDDPI (single dose)
- Treatment D Matching placebo to indacaterol via SDDPI (single dose)

Centres

3 centers in 1 country (Canada).

Publication

Not applicable.

Objectives

Primary Objective:

To evaluate the tolerability of indacaterol salts (maleate, xinafoate and acetate) in comparison to placebo in patients with mild to moderate persistent asthma.

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

Indacaterol maleate 400 µg via SDDPI (single dose)
Indacaterol xinafoate 400 µg via SDDPI (single dose)
Indacaterol acetate 400 µg via SDDPI (single dose)
Matching placebo to indacaterol via SDDPI (single dose)

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

Not applicable.

Criteria for Evaluation

Efficacy

Not applicable

Safety

Vital signs (temperature, blood pressure and pulse rate) ECG, hematology, blood chemistry, urinalysis, serum potassium and plasma glucose evaluation, adverse events and monitoring of concomitant medication use.

Tolerability

Tolerability assessments were undertaken independently by both the investigator and the patient. Criteria were reporting the presence of cough and its severity, abnormal taste, breathlessness and ease of using the device.

Statistical Methods

All patients who completed the study were included in the tolerability analyses. Endpoints were analysed using a non-linear logistic mixed effects model with treatment, period and sequence as fixed effects and subject as a normally-distributed random effect (Ezzet and Whitehead, 1991).

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Male and/or female patients 18 to 65 years old, inclusive, with mild to moderate persistent asthma.
2. Diagnosis of asthma will be based on (GINA) guidelines. FEV1 at screening >70% predicted (reversibility will not be measured).
3. Patients must have been on stable asthma treatment for at least 1 month.
4. Use of stable chronic medication will be permitted, except as noted in the study protocol
5. BMI must be within the range 18-32 kg/m^2, inclusive
6. Female subjects must have been surgically sterilized at least 6 months prior to screening. Surgical sterilization procedures must be supported with clinical documentation made available to sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the CRF.
   OR:
   Postmenopausal women must have no regular menstrual bleeding for at least 1 year prior to inclusion.
   Menopause will be confirmed by a plasma FSH level of >40 IU/L at screening.
   OR:
   Female subjects of childbearing potential must be using two acceptable methods of contraception, (e.g., intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.), from the time of screening and for the duration of the study, through study completion and for *3* months following study completion.
7. Vital signs (after 3 minutes resting measured in the supine position) not considered by the Investigator to be indicative of a disorder which would make it unsafe for subject to participate in the study or require medical intervention.
8. Able to provide written informed consent prior to study participation.
   Subject information and consent forms generated by the investigator must be approved by the sponsor prior to submission to the Ethics Committee (EC)/Institutional Review Board (IRB). A copy of the subject information and consent forms approved by the EC/IRB must be forwarded to the sponsor prior to study initiation.
9. Able to communicate well with the investigator and comply with the requirements of the study.
10. Able to demonstrate ability to use SDDPI

Exclusion criteria

1. A urine cotinine level greater then the local laboratory lowest level of quantification (LOQ of 500 ng/ml or lower).
2. Use of any antitussive medication within 2 weeks prior to dosing. Use of opiates within 4 weeks prior to dosing. Any medication must be documented in the Concomitant medications / Significant non-drug therapies page of the CRF.
3. Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation. Previous participation in a study with either the investigational or comparator drugs does not exclude a patient from participation in this study.

4. Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing.
5. Significant illness within the two weeks prior to dosing.
6. A past medical history of life-threatening arrythmias or a history, or family history, of long QT syndrome.
7. QTc (calculated according to Bazett) greater than 430 msec for males or 440 msec for females
8. History of autonomic dysfunction.
9. History of clinically significant drug allergy. A known hypersensitivity to the study drug or drugs similar to the study drug.
10. Any surgical or medical condition which in the opinion of the investigator would make it unsafe for the patient to participate in the study e.g. uncontrolled hypertension or unstable coronary artery disease.
11. Any medical conditions that would confound the interpretation of this study (eg, bronchitis, URI).
12. A diagnosis of COPD or diabetes mellitus.
13. History of being immunocompromised, including a positive HIV (ELISA and Western blot) test result.
14. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
15. Patients will be excluded if they have been hospitalized or received treatment in the emergency room for an acute asthma attack in the previous month.
16. Oral corticosteroid treatment for asthma within 4 weeks of study. (Use of inhaled glucosteroids is permitted.)
17. Use of exogenous potassium, beta-blockers, oral hypoglycemic agents, insulin or other medication which may pose glucose control issues.
18. History of left-ventricular heart failure or symptomatic coronary atherosclerotic cardiovascular disease (ie, angina, history of MI)

Number of Subjects

	Novartis product	Comparator
Planned N	100	NA
Randomized n	98	NA
Intent-to-treat population (ITT) n (%)	100 (100%)	NA
Completed n (%)	91 (93%)	NA
Withdrawn n (%)	7 (7%)	NA
Withdrawn due to adverse events n (%)	2 (2.2%)	NA
Withdrawn due to lack of efficacy n (%)	0 (0)	NA
Withdrawn for other reasons n (%)	6 (6%)	NA

Demographic and Background Characteristics

	Novartis product	Comparator
N (ITT)	100	NA
Females : males	39:59	NA
Mean age, years (SD)	37.9 (11.95)	NA
Mean weight, kg (SD)	73.3 (12.99)	NA
Race White n (%) Black n (%) Asian n (%) Other n (%)	 90 (91.8%) 4 (4.1%) 1 (1.0%) 3 (3.1%)	NA
Mean FEV1 % predicted [SD])	95.4 (13.04)	NA

Safety Results :

All formulations were well tolerated. The xinafoate and acetate salts of indacaterol showed lower event rates for local tolerability measures such as postinhalational cough, throat irritation, dry throat than the maleate formulation with the latter two symptoms being close to the placebo event rates.

Serious Adverse Events and Deaths

No SAEs or deaths occurred during the conduct of the study.

Other Relevant Findings

None

Date of Clinical Trial Report

04 Feb 2010

Date Inclusion on Novartis Clinical Trial Results Database

01 Jun 2010

Date of Latest Update

NA